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LELAND-STANFORD JUNIOR UNIVERSITY



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THE HARVEY LECTURES

DELIVERED UNDER THE AUSPICES OF

THE HARVEY SOCIETY OF NEW YORK

1912-1913

BY

PROF. MAX RUBNER
PROF. GEORGE H. F. NUTTALL
PROF. JOSEPH ERLANGER
PROF. GEORGE N. STEWART
PROF. F. B. MALLORY

MAJOR FREDERICK F. RUSSELL
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PREFACE

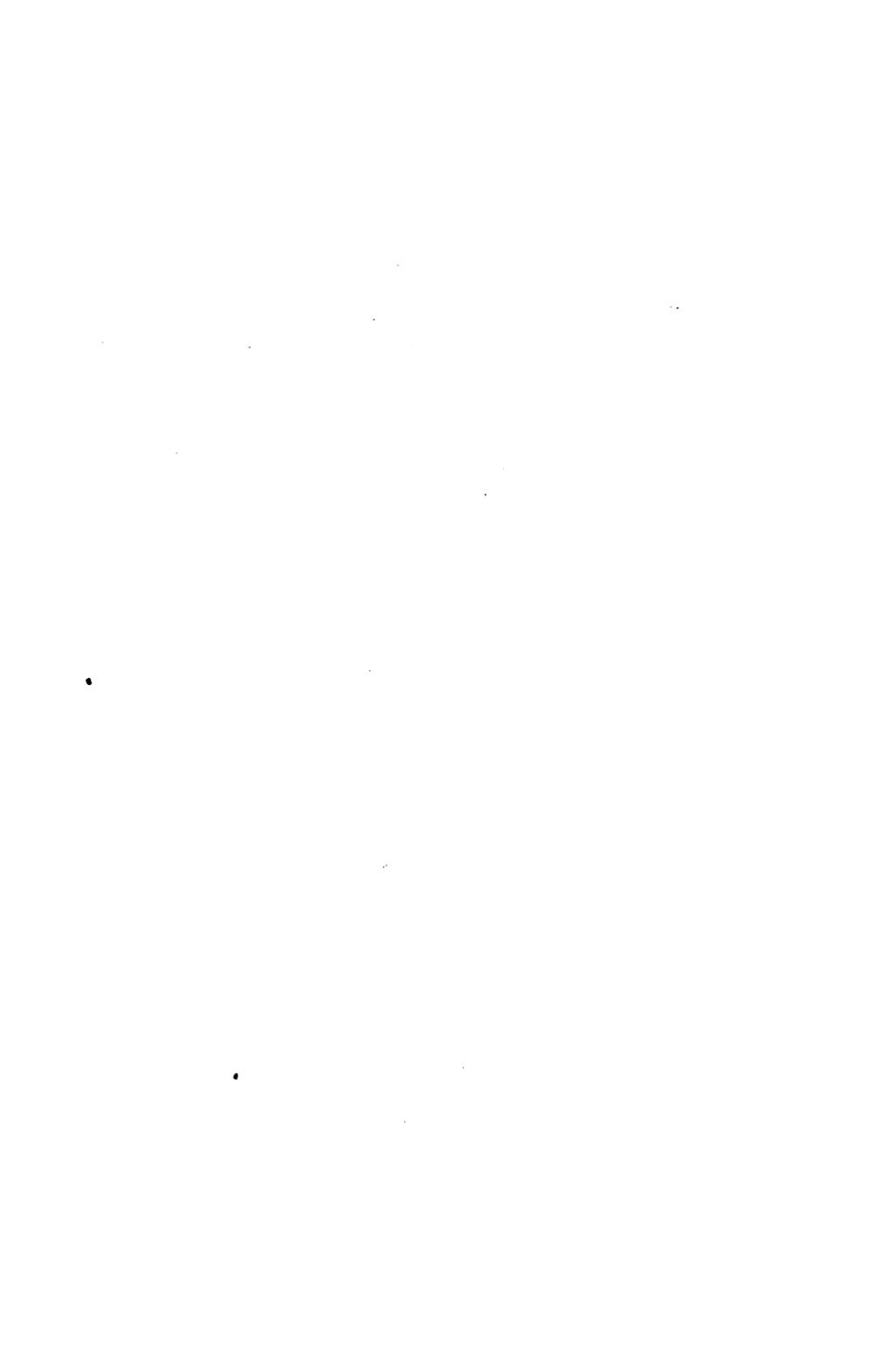
THE Harvey Society follows closely the precedents of former years in the publication of this, the eighth, volume of lectures. The generous coöperation of those who have been invited to lecture, and the continued support of its members, have enabled the Society to maintain its ideals and standards. Each year the Society has reached a larger audience. The Harvey Lectures published in this volume have all appeared in journals devoted to special phases of medical science.

The Johns Hopkins Bulletin, vol. xxiv, contains the lectures of Professor Nuttall and Professor Knoop; the American Journal of Medical Sciences, vol. cxlv and cxlvi, those of Professor Janeway and Major Russell; the Boston City Hospital Report, sixteenth series, the lecture of Professor Mallory; the Archives of Internal Medicine, vol. xi, that of Professor Erlanger; the Popular Science Monthly, vol. lxxxii, and the American Journal of Diseases of Children, vol. v, contain the lectures of Professor Conklin and Professor Howland. In Heart, vol. iii, and the Journal of Experimental Medicine, vol. xviii, portions of Professor Stewart's lecture appear, although in its present form the lecture has not yet been published. The courtesy of the Editors of these journals is gratefully acknowledged.

The Society is especially indebted to Dr. H. D. Dakin for his translation of Professor Knoop's lecture, which was delivered in German.

October, 1913.

AUGUSTUS WADSWORTH, *Secretary.*



THE HARVEY SOCIETY

A SOCIETY FOR THE DIFFUSION OF KNOWLEDGE OF THE
MEDICAL SCIENCES

CONSTITUTION

I.

This Society shall be named the Harvey Society.

II.

The object of this Society shall be the diffusion of scientific knowledge in selected chapters in anatomy, physiology, pathology, bacteriology, pharmacology, and physiological and pathological chemistry, through the medium of public lectures by men who are workers in the subjects presented.

III.

The members of the Society shall constitute three classes: Active, Associate, and Honorary members. Active members shall be laboratory workers in the medical or biological sciences residing in the City of New York. Associate members shall be such other persons as are in sympathy with the objects of the Society. Honorary members shall be those who have delivered lectures before the Society and who are neither active nor associate members. Associate and honorary members shall not be eligible to office, nor shall they be entitled to a vote.

Members shall be elected by ballot. They shall be nominated to the Executive Committee and the names of the nominees shall accompany the notice of the meeting at which the vote for their election will be taken.

CONSTITUTION

IV.

The management of the Society shall be vested in an executive committee, to consist of a President, a Vice-President, a Secretary, a Treasurer, and three other members, these officers to be elected by ballot at each annual meeting of the Society to serve one year.

V.

The Annual meeting of the Society shall be held soon after the concluding lecture of the course given during the year, at a time and place to be determined by the Executive Committee. Special meetings may be held at such times and places as the Executive Committee may determine. At all the meetings *ten* members shall constitute a quorum.

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MODERN STEAM STERILIZATION *

PROFESSOR MAX RUBNER

University of Berlin

WE live in a hygienically strenuous period. If we consider the history of hygiene for the last forty years, we may admire the great progress which has been made in the sphere of infectious diseases of every kind, in most civilized countries. Most of the epidemics that used to decimate mankind, such as variola, plague, Asiatic cholera, yellow fever, typhoid fever, diphtheria and so on, have to-day lost all their horror.

To the modern generation maladies which in our youth seemed to us matters of course appear almost incredibly ancient and belonging to the remote past. I have seen, as a young man, the great typhoid fever epidemics in my country, especially in Munich, my native town, which formerly decimated the population; to-day typhoid fever has disappeared, until, as I was told by a clinical friend, there is not sufficient typhoid fever material for the clinical lectures.

It has required hard work to produce this effect, in spite of the rapidly increasing size of our large towns. A tour, not only through a typical large city of Germany, but also through many of the smaller cities, proves how unceasing the work here has been, and how, by means of sanitation, water-supply, public cleanliness, improvement and embellishment of dwelling houses and rooms, and the building of modern hospitals, we have striven without interruption to maintain the health of the people, the most important feature of a nation.

By means of scientific hygiene combined with the technical progress of sanitary engineers, all governments and all com-

* Delivered October 5, 1912.

munities have worked unremittingly to complete this important task.

But the cause of hygiene was strengthened by legislation. The German nation and its representative, the German Reichstag, passed at first a law against the falsification of food. It was Pettenkofer, the great hygienist, and A. W. Hoffman, the great chemist, who by untiring effort achieved this success. And later, the laws guarding against the dangers to health to which the workmen in factories, foundries, mines and other industrial institutions are subjected, the laws for the protection of women and children, and at last the wonderful social achievement—the social laws—were passed by the Reichstag. To give some examples of their beneficent effect we find that during the year 1906, more than 140,000 accidents in industrial and agricultural pursuits were adjudged liable for indemnity. More than a million persons received indemnities, either as injured persons or as survivors of persons killed, and the sum total of such indemnities exceeded 140 million marks.

The indemnity from the imperial invalid insurance during the year 1906, including the imperial contribution, may be estimated at about 160 million marks. During the first fifteen years of the existence of the invalid insurance, indemnities to the amount of more than 1,200,000,000 marks were paid. The expenditures by all the sick funds of Germany for physicians, medicine and pecuniary compensation in 1905 amounted to 232 million marks yearly, and at present about a million of marks is spent every day for the social laws. As a result of the social laws, there comes the increasing need of hospitals. The services of physicians are to-day much more in demand than formerly, because the sick fund is paying all expenses, and the progress in building hospitals and in their equipment is well known. We hope in the future to build more convalescent hospitals in the larger towns, because it is desirable, in the opinion of our hospital physicians, to prolong the treatment in very many cases.

The influence of the social laws upon the diminution of the mortality of the people is important and beyond doubt. Disease

is no longer the sword of Damocles suspended over the happiness of the people, no longer the unavoidable cause of the decay of a family. How much grief and sorrow is stilled! The milliards spent for the health of the people are not only a hygienic necessity, not only a compulsory contribution given by humanity; this expenditure is also very good business. The prophylaxis and protection of health is always cheaper than the loss of national fortune by sickness and epidemics. We cannot pause in our hygienic work. Every day brings new problems, and we must strive to win new means for combating the dangers to the public health.

I have selected for my address this evening a theme from the sphere of practical hygiene. But progress even in practical affairs cannot always be expected from technic only, it springs chiefly from a foundation of theoretical knowledge. The evolution of hygiene as a science has given a most important impulse to all modern scientific work. Scientific knowledge is always the shortest way to any practical progress.

The immense success in combating infectious diseases we owe, first, to Robert Koch, by whose research and methods the most important agents of human infection have been discovered and their peculiarities recognized. But many other things, the discussion of which would lead us too far, have helped, in my country at least, to contribute to this great success.

Among the means for combating the infectious diseases, one has always been considered very effective, namely, the destruction of infectious material by disinfection.

This fundamental idea of disinfection is as old as the conception of living contagions, which in turn is many centuries old. Whoever is interested in historical studies will be able to find in ancient hygienic literature besides many superstitions many and even important precursors of our modern disinfecting methods. We know that in some parts of the world during the great pestilence in the middle ages not only were the patients isolated, but the dwellings were disinfected according to established measures which have come down to us; the walls by means of milk of lime, the floors by means of washing with wood-

lye. In 1772 Pleney published a theory concerning the etiological influence of microörganisms and the rise of infectious diseases, which agrees surprisingly with our modern views on the subject. Experiments were made, although incompletely, with chemical agents as means of disinfection. It would be unjust not to acknowledge the importance of the scientists of that time as pioneers of rational means for combating diseases. A good many interesting facts concerning this subject may be found in a book by Hermann John Pringle, general physician of the English troops who fought in Flanders, Holland and Germany in 1743-1744. In 1780 the famous chemist, Lavoisier, in a publication on prisons recommended the disinfection of clothes by means of highly heated air and that of rooms by vapors of muriatic acid by a method indicated by de Morveau in 1773. He also recommended clothes of linen and cotton, as being less attractive for the infectious agents than wool. On the whole the theory of infection then remained the same for almost a century, no considerable progress being made.

Up to the seventies of the last century dry heat was still the only means for disinfecting clothes and similar articles; for the disinfection of rooms fumigation with chlorine and sulphurous acid were still the methods most in use. The means of disinfection by solutions had been considerably improved by the discovery of carbolic acid and corrosive sublimate, but even their action was not beyond doubt. Their great importance for practical medicine and for prophylaxis was first recognized by Lister in his application of an antiseptic method. The cleaning of infected materials with solutions of carbolic acid for the destruction of infectious agents was recommended and used in various diseases. But there was not yet any uniformity in procedures or certainty in results; empiricism had not given sufficiently clear information.

The modern doctrine of disinfection, which is based on the peculiarities of the infectious agents, did not arise until the eighties, when Robert Koch and his assistants made the first systematic experiments and learned the considerable difference between the disinfecting action against spores and that against

vegetative forms of the infectious agents. Koch then hoped that disinfection would kill all infectious agents, and that is still the effect which is expected from really good disinfecting methods, although we know nowadays that pathogenic germs only very rarely form spores.

Heat was now placed in the first rank of effective agents of disinfection; I mean not only the boiling of clothes, and similar articles, which had been used long ago, but heat in some form of closed apparatus which was filled with steam. The application of steam for heating food-stuffs had first been introduced into Germany by one of your countrymen, Benjamin Thompson, who was born near Boston on the 26th of May, 1753; he lived for a long time in Munich, where he was made Count of Rumford. He is well known for his work on the theory of heat and nutrition, as well as in that of physics and social problems.

Koch showed that steam is excellent for disinfecting articles of any description—bedding, clothes. The disinfecting apparatus is a big reservoir, which can stand some pressure of steam and through which the steam passes. By this method the air is heated very quickly and after it has reached a temperature of 100° C. all living germs are killed in the shortest possible time.

I am now going to speak to you about the further development of steam-disinfection during recent years.

In the beginning steam disinfection was purely empirical, and remained on this basis for a good many years. The procedure of using steam under pressure with temperatures above 100° C. was soon given up as well as that with superheated steam. One always returned to a current of steam with or without some pressure. Steam without pressure was preferred for cheaper apparatus, for small hospitals, and similar purposes.

If one wants to progress by means of natural science one has to study the theoretical foundations. This was neglected for a long time in the doctrine of steam disinfection. The powerful action of the steam was usually explained by its great conduction of heat; others, Sambur for instance, said

that for the purpose of disinfecting any object its pores must be filled with water, otherwise no success could be expected.

To make myself understood I must first explain that there are two kinds of steam, saturated and unsaturated. Saturated steam can be produced at any temperature below 100° C. by lowering of the barometrical pressure, by working in a partial vacuum, above 100° C. by raising the pressure and the tension of the steam. Unsaturated steam is produced by heating steam which leaves a boiler above the temperature inside the boiler. Wet linen does not dry in saturated steam; superheated steam has the same action as dry air—it dries wet linen in a very short time. This shows that physically it is not the same whether saturated steam or superheated steam is used. This difference has never been considered. The more steam is superheated the more it approaches the character of warm atmospheric air. The theoretical considerations were all based on previous practical disinfecting methods. This was a grave mistake.

It is my opinion that in steam disinfection two things must be carefully separated: first, the action, from a chemical and physical point of view, of the steam on the object; second, the action of the steam on the infectious agents. I have examined these two points separately. The first question was: Does steam act as a means of disinfection only if it condenses in the pores of the object? This hypothesis, although believed in by many, is entirely wrong. The disinfection is successful even if there is no condensation of water at all. The condensation of water as fluid is in most cases not even necessary in order to heat the objects. The hypothesis of Sambur is based on the mistaken assumption that objects are warmed only if there are visible droplets of water. Let us consider this physical aspect of heating.

Bunsen constructed a so-called steam-calorimeter; a closed reservoir which is filled with steam of 100° C. temperature, into which we may put any object, a ball of copper for instance, of a certain lower temperature; the water condenses at once on the cold ball and drops into a glass underneath. At

the end of the experiment we see from the quantity of water how much heat the ball has lost.

Disinfection by steam is not generally applied to metallic objects; it is mostly used for textiles of wool, silk, linen, cotton, feathers, hair, and so on. If these materials are used for the same experiment as the copper ball we see that they do not even become moist and consequently there will be no drops of water in the glass. From this we assume that in this case the manner of heating must be quite different. I am going to give a more detailed explanation of this process later on; at this moment it is sufficient to know that there may be disinfection without perceptible condensation of water.

Another important fact to note is that the beneficial influence of steam disinfection is only exercised on objects with large *open* pores; these are quickly disinfected. Here we notice the strong action of the steam, which is superior to that of dry heat; this was first described by Robert Koch. In objects without pores the heat spreads only very slowly, by conduction.

The penetration of the steam depends upon the difference between the specific gravity of the steam and that of the air in the pores of the materials which are to be disinfected. This fact has been recognized by Walz, Gruber, Clarenbach, Frosch and Teuscher. Consequently the heating takes place as in steam-heating—the light steam enters the pores and the heavier air escapes outward. That is why the steam should always enter the apparatus at the top while air and steam should leave it at the bottom. But this explanation of the process of steam disinfection is not sufficient. We know that in spite of the usual time of disinfection and although the thermometer shows a temperature of 100° C., in a good many cases insects, like fleas and roaches, will leave the disinfecting apparatus even more lively than when they entered it.

The reasons for this are as follows: exactly as in heating rooms by steam, the steam in some parts may meet with air which cannot give way. It then finds an enormous resistance. These parts remain cold. It is possible, too, that some parts may become impenetrable to the steam owing to moisture upon

the surface—this happens chiefly in the case of linen and cotton textiles. As a result of special researches I have calculated the time which is necessary for heating different materials by steam to 100° C.—when they are *heated only by conduction*. A ball of woollen flannel, the surface of which is impenetrable to steam, with a radius of 5 cm. takes 3 hours, of 25 cm. takes 80 hours, of 50 cm. takes 325 hours, before the temperature has risen to 100° C. in the centre. This proves the necessity of porosity.

I found another still more interesting fact: the temperature in the centre of an object which is put into steam of 100° C. may rise far above 100° C.—I even measured 147.5° C. It is easy to perform this experiment. Take a skein of wool with a radius of 5 cm. and put a thermometer in its centre. Then heat the skein for some time, for instance, in dry air of 100° C. or in cold dry air, and after this put it in a steam chamber, the temperature will rise to about 140°–147° C. This simple experiment is of great importance for the theory of steam disinfection, especially as regards the manner of heating the objects.

The explanation of this is as follows: All materials that attract water, that is hygroscopic materials, including all sorts of clothes and linen, cover themselves with water; this, however, is not visible and perceptible, but is held loosely by the object, as, for instance, the water of crystallization. Our clothes always contain hygroscopic water in proportion to the percentage of humidity in the air. This improves the conduction of heat, and I found that by absorption of 1 gm. of water at an ordinary temperature 75° C. or calories of heat are set free. Added to this there is the heat produced by the absorption of steam, so that the heating by steam, as shown above, may be very considerable. One has to consider that wool may contain up to 30 per cent. of hygroscopic water, silk a little less, and the vegetable fibers still less.

If now we return to the experiments with steam disinfection we can easily understand the enormous heat in the more compact materials. On account of the high temperature the centres of such parcels do not contain saturated steam *but unsaturated steam*. This overheating will not take place if the material is

loosened, as the fibres cool quickly after having once come in contact with the steam at 100° C. These experiments give us important hints on the way in which the material ought to be exposed in the steam disinfection apparatus. It must be well loosened and should never be compressed. If the outside of a parcel of clothes or linen is too compact and the penetration by steam cannot take place quickly, this parcel shows exactly the same conditions as the copper-ball in Bunsen's steam-calorimeter; its surface is covered with water. But water of condensation must not take place in steam disinfection, at least as far as objects with large pores are concerned.

Now let us pass on to the biological phenomena concerned in the killing of bacteria and microbes. It takes place first by the coagulation of the protein. The difference between the vegetative forms and the spores consists in the fact that when fresh the former contain a considerable amount of water and salt which makes the coagulation by heat easier. The spores (we know this with certainty as far as the mould-spores are concerned) contain only hygroscopic water and very little salt. The hygroscopic water evaporating very quickly in dry heat, there remains dry protein which contains very little salt; this explains the great resistance of spores to dry heat, the protein not coagulating even at very high temperatures. I found that liquid water is not necessary for the coagulation of the protein, a certain amount of hygroscopic water is sufficient for the purpose. White of egg, when heated, coagulates, as you know, to a white substance; if it is first dried in air and then placed under steam it coagulates without loosing its yellow color.

Steam at 100° C. is also a very important chemical agent. Keratin, albumen, casein and dried bacteria yield a little carbon dioxide, ammonia and sulphuretted hydrogen, when placed in a current of steam. This proves the destructive influence of the steam. In hot, dry air this separation takes place only at very high temperatures.

What germicidal power have the different kinds of steam in reference to the freely accessible bacteria? For some time a

temperature of 100° C. was considered absolutely necessary; higher temperatures were soon given up, the more compressed steam being more expensive and often destructive to the disinfected objects. When I tried the influence of steam at 95° C. on spores, there was very little difference; at 90° C. the spores were killed only after a rather long time (12 minutes at 90° to 1 min. at 95°). At 85° C. the disinfection required more than one hour.

It is, however, not only the temperature but the saturation of the steam also that is important. One can produce at any temperature saturated and unsaturated steam. Steam at 100° C. with a saturation of 80 per cent takes five times as long to kill bacteria as does saturated steam; steam of 70 per cent saturation takes twenty-two times as long.

Now we see why different authors have obtained entirely different results in testing the germicidal power of superheated steam. If steam at 100° C. in testing is superheated after it leaves the boiler it is altered in two ways: first, its temperature is raised, which improves its action; second, its saturation is reduced, which lessens its action. At first the two influences counterbalance each other. In superheated steam of 110° C. which was made from saturated steam of 100° C. the spores lived twice as long, at 120° C. three times as long and at 127° C. ten times as long. We learn from this that success is lessened as the steam becomes drier. The impregnation of the spores with water decreases and with this decrease the disinfecting action of the steam is diminished.

Immediately after the steam has entered the apparatus, its influence on the microbes is not very considerable as the air not only prevents the steam from entering the finest pores of the objects but also hinders the absorption of water by the microbes. The steam, however, becomes more concentrated after streaming through the apparatus for some time. If there is 8 per cent air in the steam, the time required for disinfection is considerably lengthened; 20 per cent lengthens it eightfold, 37 per cent fifteenfold and so on. The purer the steam, that is, the freer from air dilution, the quicker is its action.

Disinfection by saturated steam applied to properly prepared objects of porous and non-compressed material may lead to satisfactory results and is considered the best method for this purpose. But it has the great disadvantage of not being applicable to furs, leather, fine clothes, books, furniture and so on, as it would ruin them. Other wholly insufficient disinfecting methods—rubbing with disinfecting liquids for instance, were therefore used instead.

This too is why dry heat was again taken up as a means of disinfection; but with this, one had to give up the killing of spores altogether. The disinfection by dry heat takes rather a long time but is said to give good results at temperatures of 100° to 75° C. It was especially applied to books and military clothing. But these methods in which the air is not sufficiently saturated with steam cannot be absolutely relied upon.

The discovery of formaldehyd, a new gaseous means of disinfection, meant a great step in advance for the doctrine of steam disinfection. Oskar Löw first mentioned the poisonous influence of formaldehyd on the protoplasm of plants, but not till many years later were experiments made as to the use of formaldehyd for the disinfection of rooms.

Peerenboom and I were the first to find that a certain amount of moisture in the air is necessary for the disinfecting action of formaldehyd. The different objects, wool, linen and so on, have a specific attractive influence for formaldehyd. On other objects formaldehyd is condensed only in smaller quantities. The reaction which leads to the poisoning of the microbes and which is doubtless a union of protein and formaldehyd can take place only if there is some steam, provided that the objects are dry, as is generally the rule.

All reactions being considerably accelerated by the temperature, I thought of using formaldehyd together with the undiluted steam of a disinfecting-apparatus. It would then be possible, I argued, to use steam of a lower temperature instead of the high temperature which had proved destructive. But all the above mentioned conditions of steam disinfection must of course be fulfilled. These suppositions were tested. For my

experiments an apparatus was constructed which fulfills all the conditions of steam disinfection that have been mentioned above. A considerable lowering of the boiling point by means of a vacuum allows of the production of a steam at a temperature of 50°-60° C. or even less. The steam can be condensed and is conducted back to the boiler. Technically the construction of this apparatus was not very easy.

My experiments had to answer two questions. First, there was the question whether, in a fairly high vacuum, the steam would enter the objects entirely and quickly. The circulation of the steam might be disturbed by its mixing with air in the partial vacuum, since the difference between the specific gravity of the steam and that of rarefied air is not so great as that between the specific gravity of the steam and that of normal air. However, this one disturbing influence is counterbalanced by the great purity, the lack of air, in the steam in my method, as well as by the unimpeded attraction of the steam by the hygroscopic objects, which has been proved by experiments.

The disinfecting apparatus allows the production of steam which contains a certain amount of liquid disinfecting agent. I first compared the composition of the steam with the concentration of the liquid. It would lead us too far if I should give details of the numerous experiments I made for that purpose. I will only mention briefly that the effective substance contained by the steam by no means always corresponds with the concentration of the solutions, indeed their relations are sometimes very complicated. Formaldehyd being the cheapest of all the means which I tried, I always used it for my experiments. Christian found by means of different experiments on the killing of anthrax-spores that at 50° C. the best results are obtained if 8 per cent solutions are evaporated; which means that the steam contains from 2 to 8 per cent of formaldehyd. The spores are killed in the same time as in saturated steam of 100° C. With my method very little formaldehyd is lost, as the steam and the formaldehyd can be condensed and pumped back into the boiler. Strong pneumatic pumps empty the disinfecting apparatus in a very short time until the desired vacuum is attained.

By steam-formaldehyd disinfection even the most delicate objects are not injured. At present the method has been carried to such a degree of technical perfection that large forms of apparatus, in which even whole invalid carriages can be disinfected, are in use. Steam-disinfection may now be used for all those objects to which it could not be applied formerly and it kills not only the vegetative forms of the microbes but all living germs. It is possible to construct a large apparatus for the disinfection of railway cars. The difficulty is very slight and even the most luxuriously furnished car is not injured, while all living germs are killed. It would mean a great advance in railway-hygiene if much used cars, chiefly sleeping-cars, could be disinfected now and then. It is quite certain that progress will be made in this direction. Formaldehyd will not always remain the only means of disinfection: Christian found that thymol might be used as well for the apparatus. But formaldehyd, being the cheapest means up to the present, is the best for practical use. It would be of great value to provide large railway stations at the frontiers with better disinfecting apparatus. They might be useful, not only in the case of epidemics, but for the disinfection of infectious goods—I am thinking of the anthrax danger. Nowadays, infectious goods are sent to the stations which are responsible for their disinfection. This is always a danger because of the possible dissemination of infectious germs. I believe that these new methods of disinfection will help us in many cases where the former methods were not applicable.

I hope to have proved in this lecture that theory and practice must work together, and that scientific analysis is not only necessary for practical work but may even indicate new lines for its improvement.

SPIROCHÆTOSIS *

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UNDER the term "Spirochætosis" are included those diseases of man and animals due to the spiral microorganisms known as spirochætes. I shall confine myself to those which produce blood infection—the relapsing fever—in which a remarkable periodic increase and decrease in the number of the spirochætes is observable, corresponding to alternating rises and falls of the host's body-temperature. Authority is divided as to whether the spirochætes are protozoa or bacteria, and the matter is a fruitful theme of discussion upon which I shall not enter here. Judged, however, from their pathological effects and their prompt reactions to immune sera and certain drugs, they show a pronounced affinity to protozoa and exhibit phenomena not hitherto observed in bacteria.

As in trypanosomiasis, spirochætosis is readily induced by inoculation with infected blood, and may thus be communicated almost indefinitely from animal to animal. In one series, for instance, I transmitted *S. duttoni*, with apparently undiminished virulence, through one hundred mice. Again, as in trypanosomiasis (*T. lewisi*, *T. evansi*), infection may take place by feeding.

Investigations conducted during the last few years have demonstrated conclusively that the blood-inhabiting spirochætes are, in a number of instances, transmitted by blood-sucking arthropods and I propose to deal chiefly with these results, since they are of great practical importance to preventive medicine.

* Delivered October 12, 1912.



FIG. 1.—*Argas persicus* ♀.

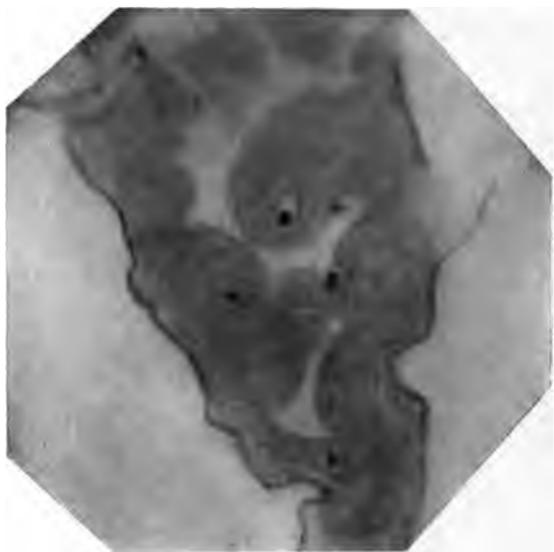


FIG. 2.—*Argas persicus*. Section of uninfected tick's Malpighian tubule. (E. Hindle.)

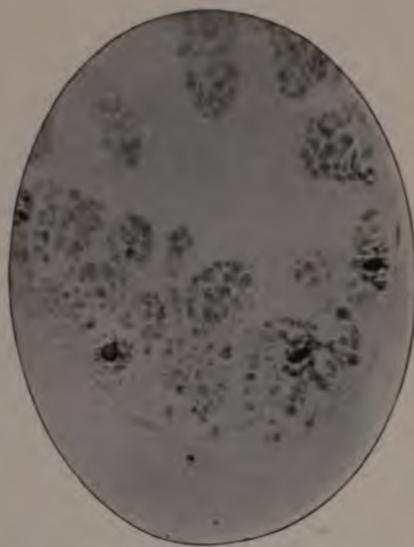


FIG. 3.—*Argas persicus*. Section of heavily infected Malpighian tubule. The cells are filled with agglomerations of coccoid bodies. (*Spirochæta gallinarum*.)

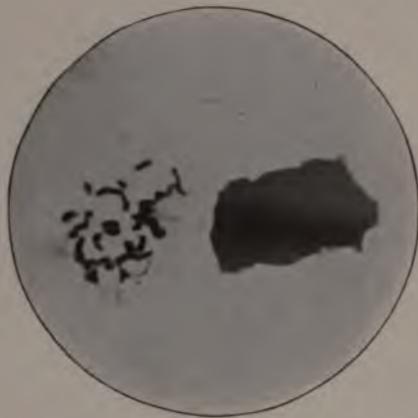


FIG. 4.—*Argas persicus*. Smear of infected ovum of the tick incubated 24 hours at 37° C. Coccoid bodies, in a Malpighian cell, developing into spirochætes. (E. Hindle & B. G. Clarke, phot.)

SPIROCHÆTOSIS IN BIRDS

In the year 1891, Sacharoff, in the Transcaucasus, demonstrated that a spirochæte, called by him *Spirochæta anserina*, was the cause of a very fatal epidemic disease in geese. The spirochætes appeared in the birds' blood shortly before the onset of symptoms, multiplied enormously, and disappeared at the approach of death. He transmitted the disease to geese and fowls by inoculation. In the year 1903, Marchoux and Salimbeni, working in Brazil, observed a similar disease in fowls, and since that date fowl spirochætosis has been recorded from many parts of the world, the causative agent being now generally known as *Spirochæta gallinarum*. We know to-day that spirochætosis in fowls occurs in southeastern Europe, in Asia, Africa, South America and Australia, and, in all places where the disease exists, is found what Marchoux and Salimbeni were the first to show to be the carrier, the tick, *Argas persicus* (Fig. 1). I have seen blood-films and determined the tick from many different places where the disease has been recorded. Personally, there is no longer any doubt in my mind as to the identity of *S. anserina* Sacharoff and *S. gallinarum*. *Argas persicus* has accompanied the fowl in its distribution in many parts of the world, but the fowl has got rid of the pest in colder climates as the tick is unable to develop at low temperatures.

Spirochætosis in fowls is a very fatal febrile disease; the mortality in a yard may attain 40-100 per cent. The disease begins with diarrhoea, followed by loss of appetite and somnolence. The birds' feathers appear ruffled, the comb pale, the birds cease to perch, and, as the disease advances, they lie prostrate upon the ground. Death may take place suddenly during a convulsive attack. The disease occurs at times in a chronic form, the emaciated birds developing paralytic symptoms after apparent recovery. Death takes place in anywhere from 3 to 15 or more days, according to the type of the disease, the body-temperature at the time of death being frequently subnormal. Whereas, in chronic cases, the liver and spleen appear atrophied, these organs are much enlarged in acute cases,

the liver showing fatty degeneration and at times focal necroses. The fowl spirochæte from Brazil kills geese in 5 to 6 days after inoculation, and produces a fatal infection in ducks, guinea-fowls, turtle-doves, and other birds.

Thanks to the kindness of Dr. Marchoux, I was able, at an early date, to confirm his and Salimbeni's results with infected *Argas persicus* (= *miniatus*), which he sent me from Brazil. Since that date, Marchoux, Borrel, and others, also Hindle, in my laboratory, have materially advanced our knowledge of the mechanism whereby the tick infects the fowl. Without wearying you with the details of each experimenter's work, I may summarize it as follows:

The ticks are best rendered infective if they are maintained at a temperature of 30-35° C. after they have fed upon blood containing the spirochæte. If kept at a low temperature, 15-18° C., the spirochaetes disappear very soon from their alimentary tract, and the ticks may bite birds repeatedly without infecting them. They may, however, be rendered infective after three months if placed at 30-35° C.; the spirochaetes then reappear in their cœlomic cavity, as may be shown by cutting off one of the tick's legs and examining the cœlomic fluid which exudes from it upon a slide.

When the spirochætes first enter the tick they soon disappear from the gut, a certain number degenerate, whilst others traverse the gut wall and enter the cœlomic cavity to circulate all over the body. A number of them die in this situation as evidenced by the frequent presence in the cœlomic fluid of pale, scarcely visible, non-motile spirochætes which are difficult to stain. The spirochætes next enter the various organs, especially the cells of the Malpighian tubules and sexual organs, in which they break up into a large number of small particles, or coccoid bodies, which multiply by fission and give rise to large aggregations which can be seen very distinctly in stained specimens (Heidenhain stain).¹ The coccoid bodies may also be found within the lumen of the gut and Malpighian tubules and in the

¹ Compare Figs. 2 and 3.



FIG. 5.—*Argas persicus*. Drawing of Malpighian tube cell of embryonic tick maintained 5 days at 37° C. showing coccoid bodies (*S. gallinarum*) developing with spirochaetes. (E. Hindle, 1911.)



FIG. 6.—*Ornithodoros moubata* ♀.

excreta. In the act of feeding, the tick occasionally voids excrement and exudes a few drops of secretion from coxal glands situated in the first intercoxal space, the fluid pouring out of a wide duct and being rapidly secreted from the freshly imbibed blood serum. As I showed with Strickland, this fluid, as well as the salivary and intestinal secretion of *Argas*, contains an anticoagulin. The coxal fluid dilutes the escaped excrement and facilitates its getting into the wound inflicted by the tick. This is doubtless the usual mode of infection, the coccoid bodies in the excrement gaining access to the blood of the host and afterwards developing into spirochætes, although the latter development has not actually been followed. Marchoux and Couvy (1912) state that infection may, however, take place without coxal secretion being voided. The bird begins to show symptoms after a period of incubation of about four days following upon the bite of the infected tick.

Although it was denied that the spirochæte of the fowl is transmitted hereditarily to the offspring of *A. persicus*, I expressed the opinion some years ago² that there was every probability that it would be found to be transmitted hereditarily as is *S. duttoni* in *Ornithodoros moubata*. Hindle has recently confirmed this supposition (Figs. 4 and 5). Coccoid bodies are found within the Malpighian cells of the embryonic tick, as described by Leishman for *S. duttoni* in *O. moubata*. If the eggs are maintained at 37° C., the coccoid bodies grow and assume a form which suggests they are on the way to forming spirochætes. The spirochæte stage occurs in the coelomic fluid of the tick, but not within its body cells. I may add here that *Argas reflexus* has been shown by Shellack (1908) to transmit the fowl spirochæte.

HUMAN RELAPSING FEVER IN TROPICAL AFRICA

Although David Livingstone (1857) was the first to report upon pathogenic effects following upon the bite of the tick we know to-day as *Ornithodoros moubata* (Fig. 6), it was

² Harben Lectures, 1908.

not until the year 1905 that Dutton and Todd, in the Congo, and shortly afterward, Robert Koch, in German East Africa, demonstrated that this tick transmitted spirochaetosis to man. The British authors made the important observation that the *Spirochaeta duttoni* is transmitted hereditarily to the offspring of the tick, a fact confirmed by Koch, who discovered that 5-15 per cent., and at times 50 per cent., of the ticks harbored the parasite. Koch captured the ticks at resting places along caravan routes and in places outside the regular routes. Apparently, owing to German East Africa having been opened to trade for a much longer period than the Congo, the tick appears to be much more widely distributed in East Africa than in the Congo. Dutton and Todd state that in the Congo it occurs only along routes of travel. I have examined a large number of specimens of this tick from various parts of Africa and would note that its geographical distribution is far wider than our present records show for the distribution of relapsing fever in man. There is every reason to fear, therefore, that an extension of the disease will follow with time, unless the natives learn even better than they do to shun the "tampan." In fact, I have an interesting observation to note in this connection which bears out my contention. It emanates from the Rev. John Roscoe, of Cambridge, who gave me the information last year. This gentleman was a missionary in Uganda, where he lived for many years at Kampala in a native-built house having reed walls supported by the usual wooden pillars. To quote his words: "Some of the pillars were in rooms, not in the walls, and it was at the bases of two of these pillars in the room used as a dining room that I noticed the ticks in the year 1896 or about that time. For several years I continued to live in the same house and suffered no harm from them. In more recent years, that is, about 1903 or 1904, both Europeans and natives have suffered from 'Tick Fever' (*Spirillum*) in houses which were built on either side of the site on which my old house stood. It has been affirmed that the ticks in these houses are the cause of the fever; I can only conclude that in previous years they were innocuous and that they have

become noxious since 1896." I do not know of any similar observation having as yet been recorded.

The disease has repeatedly been transmitted to experimental animals, rats, mice, and monkeys, by means of infected ticks, and in a number of cases unwittingly to experimenters in European laboratories. I may, in this connection, instance the case of Mr. Merriman, in my laboratory, who suffered from the disease in consequence of being bitten by two *O. moubata* (first-stage nymphs) whose biology he was studying. He did not know he had been bitten by the ticks until after two days when he showed me two characteristic bites upon his forearm. His attack followed 16 days after the bites were inflicted, the incubation period being four to six days longer than is usual.

Of 25 monkeys with which Möllers experimented in Berlin no less than 20 died of spirochætosis. There is, therefore, no possible doubt about the tick being the carrier of the disease.

Möllers' observations were of fundamental importance in relation to the etiology of the disease. He proved that ticks continue to harbor the parasite even after repeated feeds upon clean animals: thus 10 out of 12 monkeys were infected in succession by one lot of ticks which were fed upon them. His stock of ticks had died down to a low point toward the end of the series or the positive results would doubtless have continued longer. A tick may remain infective for 18 months or more after its initial infective meal of blood. He proved, moreover, that the parasites in the tick were transmitted hereditarily to the third generation when the ticks were fed throughout upon clean animals. Another observation possessing considerable interest is that of Manteufel (1910), that the ticks apparently acquire immunity to spirochætal infection. Hindle has since found that about 30 per cent. of the *moubata* sent to me from Uganda failed to become infected. It is conceivable that the stage of the disease or of the spirochæte's development at which the tick imbibes the parasites may have some influence upon the number of ticks which become infected, as noted by Miss Muriel Robertson for *Trypanosoma gambiense* in *Glossina palpalis*, to

which reference will be made in another lecture.³ Such a condition might well account for some of the immunity which is stated to occur. We know that there are marked variations in the viability of spirochaetes in relapsing fever blood preserved in vitro. Thus, Novy and Knapp (1906) found that *S. recurrentis* (American strain) survived for 30 to 40 days in defibrinated blood drawn from a rat during the onset of the disease, whereas they only survived 24 hours in blood drawn during the decline.

Although Dutton and Todd, Balfour, and others observed the breaking up of spirochaetes into minute granules in the body of ticks, Leishman was the first to follow the process more clearly. He proved that the coxal secretion was anticoagulant and non-infective, and that the excreta were infective by inoculating them into animals. He found that only when *moubata* voided excreta in the act of biting that animals under experiment became infected. He therefore concluded that the mode of infection is contaminative through the tick's excreta, and not active through its proboscis. Experiments which I carried out, and which were extended and reported upon by Hindle in my laboratory, completely confirm the results of Leishman. If the internal organs of an infected *moubata* are carefully dissected out and well washed in sterile salt solution, it is found that the gut, together with its contents, the Malpighian tubes, the sexual organs and excrement are infective when emulsified and injected into a susceptible animal. The coxal secretion always, and the salivary glands in most cases, give negative results. The few positive results with salivary gland inoculations may well be referred to experimental error in that the glands, in the process of dissection, may easily become contaminated by spirochaetes derived from other organs and be imperfectly cleansed in the process of washing. Inoculations with emulsified eggs of *moubata* have also given positive results, as might be expected, for spirochaetes have been found in them by a number of authors. Koch (1905) and Carter (1907) being among the first to demonstrate their presence microscopically in this situation.

* The Johns Hopkins Hospital Bulletin, vol. xxiv, No. 265, 1913.



FIG. 7.—*Ornithodoros moubata*. Malpighian tube of 3d stage nymph infected hereditarily with *Spirocheta duttoni*. A vast number of coecoid bodies fill the Malpighian cells. (Sir Wm. Leishman.)

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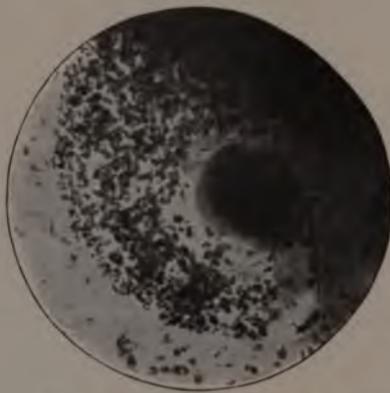


FIG. 8.—*Ornithodoros moubata*. Egg protruding from edge of ovary of infected female and heavily charged with coecoid bodies. X 1500. (Sir Wm. Leishman.)

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FIG. 9.—*Boophilus decoloratus*, ovipositing females.

After being ingested by the tick, the spirochætes usually disappear from the lumen of the gut in about nine to ten days, but they reappear if the tick is placed at 35° C. They are then found in the cœlomic fluid and their subsequent behavior is similar to that described in the fowl spirochæte (Figs. 7 and 8).

It is highly probable that other species of *Ornithodoros* play a like part in the etiology of relapsing fever in other parts of the world than those in which *moubata* occurs, the latter being a purely African species. *Ornithodoros savignyi*, which is indistinguishable from *moubata* at a casual glance, and which also occurs in Africa, at Aden, and in India, has been found by Brumpt to convey a spirochæte derived from cases of human relapsing fever occurring in Abyssinia. *Ornithodoros turicata* is suspected in connection with relapsing fever in Colombia and *O. talaje*, I have no doubt, might play a similar part in Mexico and Central America whence I have received specimens. Lately, both Leishman and myself have received specimens of *O. tholozani* from Quetta, India, where it was suspected of being a vector, but experiments carried out with the few living examples which reached Leishman have proved negative. Again, from the fact that *Argas persicus*, as tested experimentally by Sergent and Foley (1908) in the Sud-Oranais, Africa, serves as a host for spirochætes of human origin, we may conclude that this species, which frequently attacks man, may also communicate relapsing fever under suitable conditions. Sergent and Foley found the spirochætes present in the cœlomic fluid of this tick for two days, after which they disappeared.

That neither the tick nor the spirochæte are specifically adapted to each other is a matter of considerable importance which has been revealed by recent research. In view of the morphological similarity of the supposedly different species of spirochætes and their individual variations in virulence, we may well doubt if many of the "species" are valid. As I pointed out four years ago, the various specific names given to the spirochætes causing relapsing fever in man may be used merely for convenience to distinguish strains or races of differ-

ent origin.⁴ They cannot be regarded as valid names, in the sense of scientific nomenclature, for virulence and immunity reactions are not adequate tests of specificity. Under experimental conditions *O. moubata* has served for the transmission not only of *S. duttoni* and two other so-called species, *S. recurrentis* and *S. novyi*, which affect man in the Old and New World respectively, but it has also been found to transmit the fowl spirochæte. *S. duttoni*, moreover, has been successfully transmitted to rats by *Hæmatopinu pinulous*, the common rat-louse. There is every reason to suppose that a spirochæte capable of adapting itself either to a tropical African tick or a rat-louse occurring all over the world, will be able to accommodate itself to a variety of vertebrate hosts; and we know in fact, from laboratory tests, that a considerable number of animals are susceptible to infection with *S. duttoni*, various species of monkeys, rats, mice, rabbits, guinea-pigs, sheep, goats, horses, dogs, and other animals, having been successfully infected.

TRANSMISSION OF RELAPSING FEVER BY PEDICULUS AND CIMEX

It has long been supposed that vermin are responsible for the transmission of relapsing fever in Europe. Flügge (1891) appears to have been the first scientific writer to suggest this possibility and Tictin (1897) supposed that bugs (*Cimex lectularius*) might transmit the disease by their bites or by being crushed and their contents entering the skin through excoriations due to scratching. He infected monkeys with the contents of bugs removed 24 hours after they had fed on relapsing fever blood. Karlinski (1902) and likewise Schaudinn observed the survival of spirochætes in bugs for 30 days or more. Christy (1902) and Breinl, Kinghorn, and Todd (1906) failed to transmit spirochætosis by bugs. In experiments of my own (1907) it was found that *S. duttoni* survived six days in the bug at 12° C., but only for six hours at 20-24° C. Similar results were ob-

⁴ *S. recurrentis* may be the only true species; the name *recurrentis* has priority over *S. obermeieri*. Other so-called species are *duttoni*, *rossi* or *kochi*, *novyi*, *berbera*, *carteri*, etc.

tained by *S. recurrentis* (from Russia). The parasites appeared to be merely digested by the bug, the rate of digestion being governed by the temperature at which the insects were maintained. In but one experiment did I succeed in transmitting relapsing fever to a mouse by means of bugs. In this case I used 35 of the insects, and transferred them directly from an infected to an uninfected mouse, interrupting their feed upon the first animal and allowing them to complete it upon a second clean mouse. We may, therefore, conclude that bugs can occasionally transmit relapsing fever.

We have, on the other hand, conclusive proof that lice are concerned in the transmission of the disease. The first important evidence in this connection dates from Mackie (1907), in India. This author records an outbreak of relapsing fever amongst school children, in which 137 out of 170 boys and 35 out of 114 girls were attacked. The boys were found to be more infested with vermin than were the girls. An examination of the lice removed from the boys showed 24 per cent. of them to contain spirochaetes, whereas only 3 per cent. of the lice collected from the girls contained these microorganisms. As the epidemic increased among the girls their verminous condition became more evident, as the epidemic decreased among the boys the lice were found less frequently upon them. Mackie noted that the spirochaetes multiplied within the gut of the lice and that they could be found in the ovary, testis, and Malpighian tubules of the insects. He concluded that infection might result from the insects regurgitating the contents of their alimentary canal into the wound in the act of feeding.

Sargent and Foley (1908) next observed the presence of *Pediculus vestimenti* upon the persons of nearly all patients affected with relapsing fever in Sud-Oranais, North Africa, and they observed spirochaetes in the bodies of the lice. Subsequently (1910), they found these lice associated with every case they observed in Algeria.

The most convincing observations are, however, those published in a short paper this year by Nicolle, Blaizot, and Conseil (1912). They note, in respect to its epidemiology, that

relapsing fever affords a striking similarity to typhus fever. The disease extends in a similar manner, it occurs in the same places, when it enters hospitals it does not spread, sparing the nurses and physicians who have to deal with the patients who have been cleansed, whereas it attacks those who have to handle the patients at their entry into the hospital. In both diseases, as observed in Tunisia, lice are invariably found on the patients.

Nicolle and his colleagues obtained negative results when they attempted to transmit the disease through the *bites* of infected lice placed upon experimental monkeys and five persons (two of whom were the authors), although both men and monkeys were exposed to thousands of bites collectively. Upon studying the behavior of the spirochætes in the lice (*P. vestimenti* and *P. capitis*), they found that they disappear and afterward reappear. But few can be detected in the gut five to six hours after the infective feed, and some are discoverable microscopically when 24 hours have elapsed. After about 8 to 12 days, however, actively motile spirochætes reappear in the louse; at first they are short, but later they resemble those seen in the blood. Such spirochætes are observable in lice up to the eleventh day, and possibly longer. Monkeys inoculated with the contents of lice, crushed on the fifteenth day after the infective feed, developed relapsing fever.

We know that all persons infested with lice are addicted to scratching themselves, whereby they excoriate their skin and frequently crush the lice upon their bodies. In this manner their hands and finger-nails become infected with the body contents of the lice, including the spirochætes, and these gain a ready entrance through the excoriated skin, thereby infecting the individual. One of the authors, having excoriated his skin, smeared the contents of an infected louse upon the lesion, and succeeded thereby in infecting himself, the disease developing after a period of incubation lasting five days. In one experiment, infection followed the placing of the contents of a louse upon the conjunctiva in man. In nature, it might well happen that the soiled hand might travel to the eye and

produce infection in a similar manner. The authors proved, moreover, that the spirochætes are transmitted hereditarily to the offspring of the infected lice, for they found that eggs, laid 12 to 20 days after the infection of the parent lice, contained the spirochæte. The larvæ issuing from these eggs likewise contained spirochætes. By incubating the eggs at 28° C., the larvæ hatched out on about the seventh day. When the eggs or larvæ were crushed and inoculated into a monkey the latter became infected.

We still lack detailed information regarding the behavior of the spirochætes in the lice and their offspring; possibly it is similar to that recorded for *S. duttoni* in *O. moubata*. The main point may, however, be now regarded as established that lice (both *P. vestimenti* and *P. capitis*) transmit relapsing fever and are presumably the ordinary vectors in most parts of the world. These discoveries are naturally of the greatest practical importance, in view of the prevention of relapsing fever.

I shall here digress to say a few words about the biology of lice infesting man, since you will find no precise information about it in the literature, except for the observations made by my demonstrator, Mr. Cecil Warburton, in Cambridge. The latter has made the only accurate observations hitherto recorded for *Pediculus vestimenti* in conjunction with an investigation we undertook on behalf of the Local Government Board, the results of which were published in their reports for 1910. Mr. Warburton found that *P. vestimenti* (= *corporis*) lives longer than *P. capitis* under adverse conditions. This is doubtless due to its living habitually on the clothing, whereas *capitis* lives upon the head where it has more frequent opportunities of feeding. He reared a single female upon his own person with self-sacrificing enthusiasm, keeping the louse enclosed in a cotton-plugged tube with a particle of cloth to which it could cling. The tube was kept next to his body, thus simulating the natural conditions of warmth and moisture under which these creatures thrive. The louse was fed twice daily whilst it clung to the cloth upon which it rested. The female lived one month. She

copulated repeatedly with a male which died on the seventeenth day, and was replaced by a second male which likewise entered into copulation and survived the female. Copulation commenced five days after the female emerged and the process was repeated a number of times, sexual union lasting for hours. The female laid 124 eggs within 25 days. The eggs hatched after eight days under favorable conditions, such as those under which the female was kept; they did not hatch in the cold. Eggs kept near the person during the day and hung in clothing by the bedside during the winter in a cold room, did not hatch until the thirty-fifth day. When the larvæ emerge from the egg they feed at once if given a chance to do so. They are prone to scatter upon the person and abandon the fragment of cloth to which the adult clings. The adult stage is reached on the eleventh day after three moults occurring about every fourth day. Adults enter into copulation five days after the last ecdysis. The adults reared by Mr. Warburton lived about three weeks after the final moult, and the "egg to egg" period is reckoned at about 24 days. Unfed *P. vestimenti* adults died quickly at any temperature; only one specimen survived in a feeble condition until the fifth day. Unfed larvæ died in 36 hours.

To this we may add that Nicolle and his colleagues find that both *P. vestimenti* and *P. capitis* survive longest when maintained at 28° C., in a damp atmosphere, being fed twice a day.

I have allowed myself this digression, dealing with *Pediculi*, because Warburton's results are doubtless unknown to many and these parasites have only lately crept—not sprung—into prominence, especially with regard to the etiology of typhus fever and relapsing fever.

It is of importance to note how long the eggs may survive in view of the hereditary transmission of the spirochætes in lice. It is obvious that the disinfection of verminous clothing is indicated as a preventive measure, and that those coming in contact with patients suffering from these diseases should

promptly change their clothing and inspect their persons carefully after exposure, with a view to avoiding the bites of infected lice.

SPIROCHÆTOSIS IN CATTLE

The discovery of spirochætosis in cattle is due to Theiler after whom the causative agent, *S. theileri*, has been named. The parasite is transmitted by the tick *Boophilus decoloratus* in Africa (Fig. 9). Laveran and Vallée, to whom Theiler sent the infective ticks, reproduced the disease experimentally in France. That the ticks in this case become infected hereditarily goes without saying, for the infective ticks used by the French authors were larvæ hatched from eggs laid by females which had fed on cattle harboring the spirochætes in South Africa. We lack observations to show if the ticks may remain continuously infective through several generations, as seen in *S. duttoni*-infected *O. moubata*. About 14 days after such infective larvæ are placed upon cattle, the latter develop spirochætosis, but the infection appears to be mild. In Laveran and Vallée's experiment spirochætes were only present in the blood for four days. Four days later, however, the animal developed piroplasmosis, proving that the ticks had transmitted a double infection. Koch, working in Africa in the same year (1905), likewise observed spirochætosis in cattle and reported finding the spirochætes in the eggs of a species of tick which he found upon the affected animals.

This exhausts the list of spirochætes concerning whose mode of conveyance we have definite knowledge. There are, however, a number of different animals infected by spirochætes which are doubtless transmitted in a similar manner. Horses occasionally harbor spirochætes, and so do sheep in Africa, and, judging from inoculation experiments, these spirochætes are probably identical with *S. theileri*. Bats, as Nicolle and Comte found in Northern Africa, suffer from a typical relapsing fever due to *S. vespertilionis* which may be conveyed by several of the numerous ectoparasites infesting these animals; *Argas vespertilionis* and lice would naturally suggest themselves to

me as being the probable vectors. *Spirochæta muris*, occurring in rats and mice, and *S. gondi* Nicolle, 1907, occurring in a small African rodent (*Ctenodactylus gundi*) are both transmissible by blood inoculation and presumably in nature are transmitted by ectoparasitic arthropods.

CULTIVATION OF SPIROCHÆTES

Another important step in our knowledge concerning spirochætes is that they can be cultivated in vitro. All efforts to cultivate them under ordinary conditions, suitable for the great majority of bacteria, have given negative results in the hands of many bacteriologists all over the world. Levaditi (1906), it is true, succeeded in cultivating *S. gallinarum* and *S. duttoni* in collodion sacks placed, according to the usual technic, in the peritoneal cavity of rabbits. Under these conditions the spirochætes multiplied and lived for 73 days or more. Successful cultivation in vitro has, however, only been recently accomplished by Noguchi (August, 1912) by adding a few drops of citrated rat or mouse blood, containing the spirochætes, to sterile ascitic or hydrocele fluid (10 to 15 c.c.) in tubes containing pieces of freshly excised rabbit's kidney. Precautions against bacterial contamination are imperative; it is best to collect the infected blood at the 48th to the 72d hour of the disease, and the tubes should be maintained at 36° C. He experimented with *S. duttoni* and two strains of *S. recurrentis* which he calls *kochi* and *obermeieri*. *S. duttoni* was still virulent after the ninth transplantation; *S. kochi* was transplanted 29 times, subcultures being made every four to nine days, the maximum growth being attained about the ninth day. This strain appeared to lose its virulence by prolonged culture. *S. obermeieri* attained its maximum growth on the seventh day, and was still virulent after having attained the seventh subculture.

To sum up, then, we have represented in the blood-inhabiting spirochætes of warm blooded animals a group of micro-organisms which, under natural conditions, are mainly conveyed by blood-sucking ectoparasites within which they undergo

a process of development and in which they are hereditarily transmitted. Spirochætes are not specialized parasites. Infection may take place through the skin or mucous membrane to which the spirochætes gain access by being deposited thereon in the arthropod's dejecta or by the infested individual scratching or rubbing himself with hands which have become contaminated with the contents of the vermin which they have crushed. The lesions produced by the bites of the arthropods and the excoriations inflicted upon the individual by himself greatly facilitate the entrance of the spirochætes.

THE LOCALIZATION OF IMPULSE INITIATION AND CONDUCTION IN THE HEART*

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INTRODUCTION

IT has ever and quite naturally been true that the discovery of a new structure immediately has started an effort on the part of investigators to determine the function thereof, and conversely, that the discovery of a new function or property has initiated an effort to discover some structure that could be made the seat of such function or property.

The history of the localization of impulse initiation and impulse conduction in the heart illustrates in a striking manner these tendencies and their effects. The heart is spontaneously rhythmical. Does it contain a definite structure whose purpose it is to initiate this spontaneous rhythm? Or, again, in the heart, impulses are carried from one part to another. Is this the function of a special structure? Conversely, a structure is found in the heart which conceivably might act as pace-maker, while still another is found which might well serve to carry the excitation waves from point to point in the heart. At once experiments are devised with the object of obtaining answers to these questions. Nothing could be more logical, nor in the long run more certain of gaining the goal than such a course. Nevertheless there is a danger, very well illustrated by the history of these subjects, of accepting the bare inference in either direction as a fact, or of accepting as conclusive experiments which by the investigators themselves are regarded only as suggestive, or, owing to the reasonableness of the inference, there even is a danger that the investigators themselves may be

* Delivered November 9, 1912.

led to draw conclusions from evidence which at the time is obviously insufficient, or which time may show to have been insufficient.

While the main purpose of this paper is to review critically the work that has been done in the effort to localize the functions of impulse initiation and conduction in the heart, it is hoped that it will at the same time serve to illuminate the way to some of the pitfalls and dangers and difficulties that beset investigators in this field of physiology.

I. THE LOCALIZATION OF IMPULSE INITIATION

HISTORICAL

The earliest attempt to account for the regularity of the heart's action led the older physiologists into all sorts of futile hypotheses. Down to the year 1813 the term "*organic instinct*" was employed to designate it.¹ Long before this date, however, physiologists were in the possession of facts which might have sufficed for a generalization closely approximating the truth as we now see it. Thus Harvey and some of the older anatomists observed the movements of the *venae cavae* to continue in some of the lower animals after the auricles had ceased to move. In the search for the *ultimum moriens* of the body, Haller, and perhaps others before him, discovered that in cold-blooded animals the right auricle usually survives death of the organism longer than other parts of the heart. This survival, however, was not attributed to any property of the tissue of the heart, but was thought to be due to the fact that after death the right side of the heart generally contains a greater or less quantity of blood which was supposed, in the time of Haller, to supply the stimulus to the heart.

Much later, in 1811, Nysten was able to confirm Haller from a study of the human species after decapitation by the guillotine. Nysten, indeed, went one step farther; he studied the irritability of various regions of the human heart, using gal-

¹ Reid: In Todd's Encyclopedia of Anatomy and Physiology, London, 1839, p. 607.

vanism as the stimulant and found that usually "those parts of the auricle around the entrance of the *venæ cavæ* retain their contractility longest."

The sequence of the heart beat in both warm- and cold-blooded animals was also known at this time. But rather than refer this sequence to any definite structure in the heart and possibly under the influence of the iatromechanists, mechanical rather than physiological explanations of the orderliness of the contractions were sought. For instance, according to Haller and Senac, the usual sequence of the several chambers is exactly what one would expect if the blood is the "habitual stimulant on which the movements of the heart depend." In view of the fact that the contraction of the heart occurs in the order in which the blood flows into its different cavities, this conclusion seemed quite satisfactory. The regular sequence of the auricles and ventricles of the empty heart was attributed by Reid,¹ in 1839, to mechanical stimulation of the empty ventricle by the tug of the auricles. Although Reid apparently was not able to free himself entirely of the influence of the prevailing hypotheses, he, nevertheless, records an experiment which led him to suggest in a vague fashion another possible explanation of the sequence of beat. He discovered that an empty heart would beat when all stimuli were removed by placing it in the exhausted receiver of an air pump, and concluded that "we are almost obliged to have recourse to the supposition that there is some innate power in the heart itself."

As an example of another type of mechanical explanation of the transmission of the impulse along the heart may be mentioned here in passing one suggested by Kürschner² in 1850. Kürschner ventured to suggest that the valve musculature, which is described in the second part of this paper, by pulling on the ventricles, and thus putting into motion a complex mechanism, determines the sequence of the auricles and ventricles.

¹ Kürschner: Wagner's Handwörterbuch der Physiologie, Braunschweig, 1850, p. 80.

The experiment of Stannius, described in 1852, has done more, however, toward putting physiologists on the right track than any other contribution to this subject. Stannius, it is well known, separated by means of a ligature the sinus from the auricles in the frog's heart and found that the sinus then continued to beat with undisturbed rate, whereas the subjacent parts of the heart came to rest. It was this experiment, as interpreted and built upon by Gaskell, Engelmann and others, forty or more years later, that finally led to the conception that the pace-maker is a part of the heart itself, and that part, namely, the sinus region, which possesses the highest grade of rhythmicity. Before this conclusion was generally accepted, however, the view had first to be overcome that the beat of the heart is dependent on the ganglia, described by Remak shortly before Stannius reported the results of his ligature of the heart. It was Gaskell who showed that in the frog's heart rhythmicity is not located in the ganglia, but "in those parts of the heart muscle which remain least altered both in circular arrangement of their fibres and in their physiological status."

We may be permitted to recall in this connection a recently closed chapter in the physiology of the heart, because it illustrates so well the pitfalls in the path of our efforts to attach function to a likely structure. Kaiser,³ in 1894, reported that if the frog's heart is brought to a standstill by tying off the sinus, a single stimulus applied to the surface of either the auricle or the ventricle is followed by only a single response; whereas if the stimulus be applied in the region of Bidder's ganglion in the auriculoventricular ring, each single stimulation is followed by a series of rhythmical contractions. He then goes on to say that "if Bidder's ganglion be removed, stimulation in the region which before aroused a series of responses now gives only one response for each stimulus." Kaiser, therefore, regarded the ganglion as the rhythmical centre of the heart. Gaskell has since shown, however, that Kaiser's conclusions were based on faulty experimentation. By working more carefully, Gaskell

³ Kaiser: See Martin, Johns Hopkins Hosp. Bull., 1905, xvi, 380.

proved that Bidder's ganglion might be pierced with a needle without causing any contractions of the heart; whereas the slightest prick of the muscular tissue in the auriculoventricular groove would give rise to a series of contractions. Obviously Kaiser had stimulated the heart tissue subjacent to the ganglion, though he believed he was stimulating the ganglion only. It is hoped that subsequent sections of this paper will serve to show how closely akin to this problem and to the methods of solving it, is the problem of impulse initiation as it presents itself to us to-day.

ANATOMICAL

The recent impetus given to the attempts to localize a pacemaker of the heart is perhaps due more to certain recent advances in the anatomy of the heart than to any other one cause, and we must, therefore, first direct attention to the light which has been shed on our subject by the efforts of anatomists.

Of the primitive hearts, that of the eel is selected as a type, owing to the care with which its physiology has been studied, and because it seems to elucidate especially well some of the problems with which this paper deals. This heart⁴ comprises three contractile cavities, the sinus venosus, the auricle and the ventricle. The arrangement and relations of these chambers are shown diagrammatically in Fig. 1. At the junction of the sinus with the auricle the whole circumference of the sinus wall does not terminate directly in the proper auricular tissue, for here the proper auricular tissue does not form a complete chamber, its floor being made up of what appears to be a direct prolongation of the ventral wall of the sinus. The auricle is not directly continuous with the ventricle; there is a short intervening tubular communication resembling the canalis auricularis. This connection is effected by means of an extremely narrow and prolonged strand of muscle fibres which is prolonged from the muscular wall of the auricular canal, and, penetrating a con-

⁴ McWilliam: *Jour. Physiol.*, 1885, vi, 192, from which what follows is largely quoted.

siderable amount of connective tissue which lies in that situation, at length becomes continuous with the muscular substance of the ventricle. The muscular continuity between the canalis and the ventricle is established by means of a remarkably long and slender isthmus of muscle substance which becomes continuous with the central fibres of the ventricle. In an effort to show the relation of the mammalian heart to that of the eel, Fig. 2 has been evolved. We do not mean to maintain that the assumptions involved in this diagram would pass muster before a comparative anatomist. Be that as it may, the diagram has proved of great service in the attempt to unify the contributions to the subject of impulse initiation and conduction.

Inasmuch as the sinus is the pace-maker of the cold-blooded heart, it behooves us first to determine what becomes of the sinus in the evolution of the heart to the mammalian form. The embryological method of determining this matter has been pursued by His.⁵ His investigations have shown that in the course of development the counterpart of the sinus venosus of the cold-blooded heart becomes in the human heart the part of the right auricle which His designates the sinus reuniens.⁶ One portion of the sinus, namely, the coronary sinus, according to His, persists as an easily distinguishable structure; the right horn of the sinus, however, sinks deep into the auricle, and the walls of these two regions become fused to such an extent that anatomists, to quote, "as yet have had no occasion to designate the sinus as a definite part of the heart." Nevertheless, its limits are distinguishable at all ages. Externally it is delimited on the right by the sulcus terminalis, a groove on the surface of the heart just to the right of the opening into the auricles of the superior and inferior venæ cavæ. On the inner surface of the auricle corresponding with the sulcus terminalis is a ridge, the tinia terminalis. To the right of this ridge the wall of the auricle is

⁵ His: *Anatomie menschlicher Embryonen*, Leipzig, 1880, p. 148.

⁶ The terms sinus reuniens and sinus venosus will be employed interchangeably.

roughened by the pectinate muscle; to the left it is smooth. This smooth part is the region of the sinus reuniens. By the comparative anatomical path, as pursued by Keith and Flack,¹ the sinus in the adult mammalian heart has been found to have practically the same contour. These investigators also state that in the mammalian heart the greater part of the sinus is submerged by an overgrowth of muscular tissue of other regions.

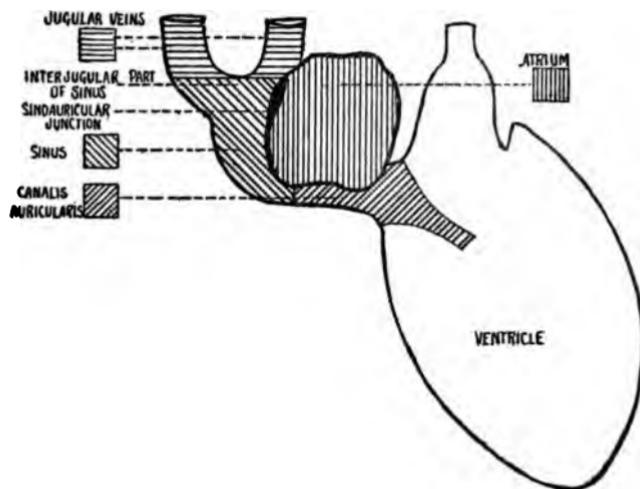


FIGURE 1

FIG. 1.—Heart of the eel. Diagrammatic. Modified from McWilliam.

According to Keith and Flack, "two parts only are left exposed on the surface of the heart: (1) the musculature of the superior vena cava, (2) the musculature of the coronary sinus."

We may therefore conclude that in the mammalian heart the remnants of the sinus venosus are to be found in an extensive area of the right auricle. Roughly, this area may be said to occupy the region between and including the superior vena cava above and the coronary sinus below, and to extend from this re-

¹ Keith and Flack: *Jour. Anat. and Physiol.*, 1907, xli, 172.

gion to the insertion of the interauricular septum into the auriculoventricular junction (Fig. 2). The amount of sinus tissue persisting is not made clear; presumably but little remains.

In the same paper, Keith and Flack describe the structure now known as the sinus node or the node of Keith and Flack. This node, owing largely to the suggestion thrown out by Keith

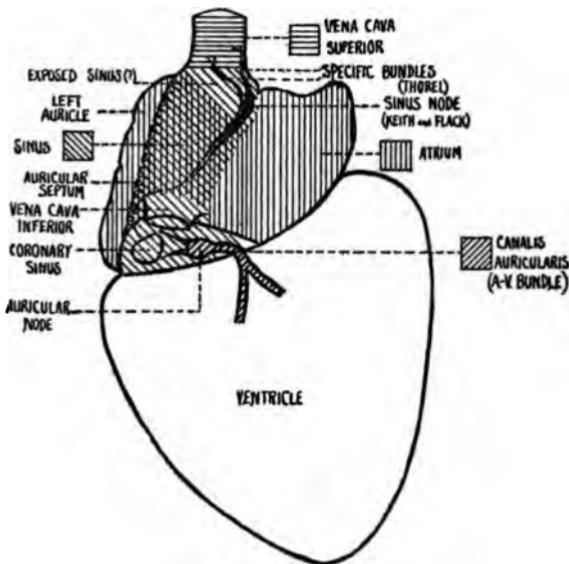


FIGURE 2

FIG. 2.—Mammalian heart. Diagrammatic. Figs. 1 and 2 are drawn to show schematically the probable homologies of the cold-blooded and warm-blooded hearts.

and Flack to the effect that in it "the dominating rhythm of the heart normally begins," has since assumed great prominence in the literature of the subject of impulse initiation, whole volumes having already been written on it. Originally described as "numerous peculiar muscle fibres, some nerve cells and nerve fibres" surrounding the artery lying in the sino-auricular junction and located in the groove termed by His the sulcus terminalis, this node, or, perhaps, the so-called specialized tissue of

this region, has with further investigation assumed a more definite form, and what is of greater significance in the interpretation of the results of experimentation, has grown in extent and complexity. Thus Koch⁸ has shown that it is club-shaped; a distinct enlargement, known as the head, sending a few fine strands back into the angle between the superior cava and the right auricular appendix, and a long tapering process downward to terminate midway between the superior and inferior cavae (Fig. 2). Thorel,⁹ on the other hand, describes not alone a structure of this form, but in addition many strands beginning as loops around the superior cava, and extending downward as far as the coronary sinus (Fig. 2). The fibres of the node communicate freely with the heart muscle fibres that surround it. It is important to bear in mind that the sinus node is not the sinus venosus, but is a so-called specialized tissue lying in the sino-auricular junction.

Although the discussion of the anatomy of the auriculoventricular bundle is reserved for the second part of this paper, it is necessary to state here that this structure is now believed to be a remnant of the part of the primitive heart-tube, known as the canalis auricularis, which unites the sinus venosus with the ventricle. It consequently should be termed the sinoven-tricular instead of the auriculoventricular bundle.

PHYSIOLOGICAL SECTION

GENERAL LOCALIZATION IN THE MAMMALIAN HEART

In the past the study of the heart beat in cold-blooded animals has been of inestimable service in the elucidation of the functions of the warm-blooded heart. Experience of many years has shown that practically all of the findings obtained from the study of the former can be applied with but slight modification to the latter. Such knowledge of the site of normal impulse

⁸ Koch: Med. Klin., 1911, No. 12.

⁹ Thorel: Verhandl. d. deutsch. path. Gesellsch., 1910, p. 71.

initiation as we have gained from observation of the cold-blooded heart should, therefore, be of service to those who are now concerned with this problem as it applies to the warm-blooded heart. In cold-blooded animals the beat starts in the great veins above the point where they unite with the sinus venosus, or if not there, certainly not below the sinus venosus.¹⁰ In view of the picture by Keith and Flack indicating that in the turtle's heart there is at the sino-auricular junction a collection of tissue which closely resembles the sinus node of higher animals and seems to be its homologue, we wish to lay special stress on the fact that the beat of the turtle's heart does not begin in the sino-auricular junction. Just what becomes of the great veins in the evolution of the heart has not, so far as I am aware, been determined. Presumably they become incorporated with the sinus in the wall of the right auricle. We should, therefore, expect the beat of the mammalian heart to begin in the right auricle in the region of the sinus venosus, or in the veins opening into it; not at the sino-auricular junction.

RHYTHMICITY OF THE RIGHT AURICLE

Attention has already been called to the observation of Nysten to the effect that the right auricle is the part of the heart of man that longest preserves its irritability to the constant current, and that for a long time this region was known to be the *ultimum moriens* of the body. That the right auricle is the most rhythmical part of the mammalian heart can be demonstrated in a striking manner by severing functionally the right auricle from the rest of the heart, but leaving its nutritive connection with the heart for the most part undisturbed. When this is done the right auricle invariably beats more rapidly than the rest of the heart.¹¹ When the functional

¹⁰ Meek and Eyster: Am. Jour. Physiol., 1912, xxxi, 31.

¹¹ Fredericq: Acad. roy. de Belg. Bull. de la cl. sc., 1901, p. 126; ref. Arch. Internat. de Physiol., 1912, xii, 109; Erlanger and Blackman: Am. Jour. Physiol., 1907, xix, 125.

separation is not quite complete a partial block may develop, every other or every third beat of the right auricle determining a beat of the rest of the heart.¹² It is of interest in this connection that the left auricle, when severed from the rest of the heart by the same method, usually ceases to beat at once and definitively. It is therefore obvious that the part of the heart in which the sinus venosus lies buried, normally determines the beat of the heart.

EXACT LOCALIZATION IN MAMMALIAN HEART

GENERAL REMARKS

In considering the efforts directed toward a more exact localization of the site of impulse initiation reference may at once be made to the view, which now is widely considered a demonstrated fact,¹³ that the sinus node of Keith and Flack is the normal pace-maker of the heart. At the very beginning of the discussion of this subject we wish to call attention again to certain *a priori* considerations that are opposed to this view. The sinus node lies in the sino-auricular junction; if it is the pace-maker it would therefore follow that in the mammalian heart the beat begins in this junction. This, we have seen, is not the case in lower forms. It should be borne in mind, however, that the last word has not yet been said with regard to the anatomy, or better, perhaps, with regard to the homologies of the sinus node. According to Koch's latest description, the node in the dog is two or more centimetres long, while Thorel claims that the so-called specialized tissue of this region is not confined to the sinus node of Keith and Flack, but occurs in a rather extensive area; an area, it would seem, that is almost coterminous with the sinus region (Fig. 2). If the latter view should prove to be correct, then to say that impulse initiation is localized in the specialized tissue is tantamount to saying that

¹² Erlanger and Blackman: Am. Jour. Physiol., 1907, xix, 125.

¹³ See, for example, Howell, Text-Book of Physiology, Phila., 1911, Ed. 4, p. 529.

it is localized in the sinus. However this may be, in the attempts to determine whether or not the sinus node is the normal pace-maker, practically all investigators have had before them the node as pictured by Koch.

INSPECTION

The first effort toward a more exact localization of impulse initiation in the warm-blooded heart was made by McWilliam¹⁴ in 1888. McWilliam observed that, in the dying heart, spontaneous contractions begin either just at the point of union of the great veins with the heart, or in the wall of the veins a short distance above this point. The same method of observation in the hands of other investigators has yielded a somewhat similar result. Thus in the dying heart of the rabbit, Hering¹⁵ found that contraction waves may start in the region of the mouths of the two superior cavæ, and in the dog's heart¹⁶ usually at the mouth of the superior vena cava; occasionally, however, at the mouth of the inferior vena cava. Fredericq¹⁷ finds that in the dog the impulse starts in the right auricle between the two cavæ. I have often watched for the spot from which the last or the first impulse starts in the dying or reviving heart, respectively, of mammals,¹² but have never succeeded in making a finer localization than to the region of the great veins as a whole. Finally Koch has concluded from observations on the heart of still-born human foetuses that the beat starts in the coronary sinus. It is, therefore, obvious that inspection of the heart certainly locates the site of impulse initiation in the region of the sinus venosus, possibly nearer to the superior than to the inferior cava. A finer localization by this method does not seem to be possible. It should be borne in mind, however, that the logic of this method of determining the normal cardiomotor area is not entirely clear. It serves to locate the most viable

¹⁴ McWilliam: *Jour. Physiol.*, 1888, ix, 167.

¹⁵ Hering; *Pflüger's Arch. f. d. ges. Physiol.*, 1900, lxxxii, 21.

¹⁶ Hering: *München. med. Wehnschr.*, 1909, lvi, 845.

¹⁷ Fredericq: *Arch. internat. de physiol.*, 1906, iv, 60.

parts of the heart, not those possessing the highest rate of rhythm, which, after all has been said, is *the* property that determines the seat of origin of the contraction wave.

RHYTHMICITY OF DIFFERENT REGIONS OF THE RIGHT AURICLE AS DETERMINED BY EXCISION AND BY STRIPS

The above-mentioned experiments show that the most highly rhythmical portion of the heart is the right auricle. Are all parts of this region equally rhythmical, or are certain parts more rhythmical than others? By excising in various ways various parts of the auricles of the perfused cat's heart and noting the effect on the heart rate, it was shown¹² in 1907 that the region of the great veins probably possesses the highest grade of rhythmicity, but that the rhythm of this region exceeds but little that of the coronary sinus region. It was pointed out, however, that this method is open to the objection that the cuts, by altering the distribution of the perfusion fluid to the several parts of the auricles, might have altered the rhythmicity of neighboring parts. Three years later it was discovered that strips of the cat's, rabbit's and dog's auricle, when excised, placed in a bath of Locke's solution, and occasionally stimulated tetanically, would give a beautiful series of beats, and for hours, provided, however, that the strips contained tissue from that region of the right auricle which approximately coincides with the sinus reuniens of His.¹³ These experiments furnish further evidence in favor of the view that the beat is initiated in the sinus region. But what is of greater significance to the present discussion is the observation made by the aid of this method that the regions of the superior vena cava, of the inferior vena cava and of the coronary sinus possess approximately the same grade of rhythmicity. Within the last few months this observation has been completely confirmed by Moorhouse,¹⁴ who, in addition, has controlled his experiments by exactly localizing the sinus node by means of serial sections.

¹² Erlanger: Am. Jour. Physiol., 1910, xxvii, 87.

¹³ Moorhouse: Am. Jour. Physiol., 1912, xxx, 358.

His experiments show in a striking manner that a strip containing the sinus node as compared with strips made from the auricle just below the node or just posterior to the node, is far from exhibiting a constant predominance of rate.

Furthermore, it has been found that stimulation of auricular strips is frequently followed by an acceleration of the rate of their beat.¹² Such an acceleration is obtained, however, only when the part of the strip stimulated is from the sinus region of the heart. In their analyses of the functions of the various parts of the cold-blooded heart, Gaskell, Engelmann, McWilliam and others, lay the greatest stress on this reaction of heart muscle to stimulation, maintaining that it is characteristic of highly rhythmical tissues. However this may be, it cannot be without interest that in the mammalian heart this response is obtained, not alone from the region of the sinus node, but from the whole of the sinus region.

EVIDENCE FURNISHED BY ACTION OF DRUGS ON STRIPS

Inasmuch as a great deal of stress is laid in this paper on evidence furnished by strips of the auricles beating in Locke's solution, it is of prime importance to prove that such evidence is valid. In the case of the cold-blooded heart, strips have for many years been employed for the purpose of determining the properties of the various parts of the heart, and of interpreting the response of the heart to stimuli of all kinds. So far as I am aware, all of the material thus obtained has been accepted by physiologists without question as applying to the whole heart. Nevertheless we must be prepared to show that mammalian strips do react as does normal heart muscle. Moorhouse is now engaged in an effort to gather evidence bearing on this question. His main method is to study the behavior of strips when bathed in Locke's solution to which various of the so-called heart drugs are from time to time added. Although this research is not yet completed, it has proceeded far enough to justify the statement that the strips containing sinus tissue respond exactly as does the whole heart to drugs which are

supposed to act on muscle tissue as well as on the nervous tissue. Of the latter group, nicotin, which is supposed first to stimulate and then to paralyze the terminals of preganglionic fibres (inhibitory fibres here), first inhibits and subsequently accelerates the strips just as it does the whole isolated heart. Pilocarpin, which slows the whole heart, presumably by stimulating the vagus terminals in the heart muscle, also slows the strips, and this action can be prevented as in the whole heart by atropin. Atropin given alone causes the well-known acceleration by paralyzing the vagus terminals, and epinephrin causes the usual acceleration, presumably by stimulating the accelerator terminals in the muscle. Of the drugs whose prime action presumably is on muscular tissue, all that have been tried, namely, caffein, the digitalis group and aconite, increase the rate of the beat and the tone of strips as well as of the whole heart. There can be no doubt, therefore, that the auricular strips behave like the perfectly normal intact auricles.

Great emphasis has been laid by all writers who have dealt with the histology of the nodes, on the presence in them of what is termed *specialized* tissue. The nodes have peculiar histological characteristics, which are designated "embryonic." It is assumed by many of these authors that "embryonic" tissue is more rhythmical than other heart tissue, and that consequently the nodes are the motor centres of the heart. Now to come to the point, if this tissue is specialized in the direction of rhythmicity, the sinus node, or the strip containing it, should not alone be more rhythmical than companion strips containing no nodal tissue, which we have seen is not the case, but in addition it should show a *specialized* response to the heart drugs. It has been found by Moorhouse, however, that if there is any difference at all in the behavior of the strips toward the drugs above mentioned, it is in the direction of greater rhythmicity on the part of the companion sinus strips, not the nodal strip. We may, therefore, conclude with the statement that if it should eventually be proved that the sinus node is the motor centre of the heart it would not have this function by virtue of its rhythmical properties.

SIGNIFICANCE OF SLOWING AND STOPPAGE FROM EXCISION OF
THE SINUS REUNIENS

Another method extensively employed in the effort to localize the pace-maker of the heart has been to determine whether or not there is a definite and fixed area, excision of which invariably stops the heart, or permanently slows its rate. The interesting results that this method has yielded have usually been applied to the problem in hand without bearing in mind all of the possibilities in the case. It is appreciated that the most plausible explanation of loss of activity following removal of a part of an organ is that the part removed determines that activity. Nevertheless, this is by no means the only explanation; it is conceivable, for instance, that such a removal may result in the establishment of a block between a region of high and of low rhythmicity under which circumstances the latter region, as is well known, will temporarily stop beating and then, after the awakening of its inherent rhythmicity, begin to beat again, though more slowly than before. It is also conceivable that as a result of injury or of partial removal, the function of the parts remaining may be altered or annulled temporarily for reasons that at present are not entirely clear. The central nervous system offers interesting and familiar examples of temporary loss of activity in parts not directly injured or removed. Thus, immediately after the onset of hemiplegia, all of the underlying reflexes are abolished, the paralysis is flaccid; soon, however, the reflexes return and the paralysis then becomes spastic.

The heart itself offers a familiar instance of the wide-spread, and at present inexplicable, effect of local injury or stimulation. It is a well-known fact that momentary stimulation of any point on the auricles or on the ventricles may throw the whole of the corresponding chambers into fibrillation. It has been shown by Garrey²⁰ that this continued incoördination is not due to any influence emanating primarily from the site stimulated. For if the area that was stimulated be excised while

²⁰ Verbal communication.

fibrillation is continuing, the incoördination of the heart does not stop; whereas the area excised, namely, the one that was stimulated, may at once cease to fibrillate.

With this analysis in mind we may review first the result on the rate of the heart beat of excision of the sinus region and of the sinus node. Excision of the whole sinus region is in effect the first ligature of Stannius, by which the sinus of the frog's heart is functionally separated from the rest of the heart. In this experiment, it will be recalled, the sinus continues to beat, whereas the subjacent parts cease beating for some time. When eventually the distal parts begin to beat it is usually with normal sequence and a slow rate. It is obvious that, owing to the complete fusion of the sinus with the auricle, the exact repetition of this experiment is not possible in mammals. For to remove all sinus tissue would involve removing practically all of the right auricle, with the exception of the appendix and neighboring tissue, down to and including the beginning of the auriculoventricular bundle. The Stannius experiment has, however, been approximated in mammals. In 1907 it was shown ^{11, 12} that in the dog's heart *in situ* clamping off all of the region of the great veins with a specially devised clamp may result in a temporary stoppage of the heart, and occasionally, perhaps, a persisting slight slowing of the heart rate. In the perfused heart it was shown that excision of this region frequently, although by no means invariably, results in transitory stoppage of the parts of the heart below it, which, after recovery, usually beat at a permanently slowed rate.²¹ These experiments were performed before the node of Keith and Flack was described; there is not the slightest doubt, however, but that the sinus node was invariably included in the tissue removed. It happens not infrequently that this operation is followed by the disappearance of the as-vs pause, the auricles and ventricles contracting synchronously instead of in sequence. But of this particular subject more later.

²¹ This result differs materially from that previously reported by Langendorff and Lehmann (Arch. f. d. Ges. Physiol., 1906, lxii, 352) but has been abundantly confirmed by others.

EFFECT OF EXCISION OF THE NODE

Since the node was described in 1907, attention has been directed to the effects of removing the region containing it alone, as compared with the removal of other regions. The results reported seem to be most inconstant. Flack,²² one of the discoverers of the node, and Jäger,²³ experimenting with the dog's and the cat's hearts *in situ*, report totally negative results when the nodal region is excised or destroyed by heat. These experiments were carefully controlled by histological examination. Magnus-Alsleben²⁴ also reports totally negative results in the perfused heart of the rabbit. Lohmann²⁵ applied formaldehyd solution to the region of the node and obtained a slowing of the heart rate. It is scarcely necessary to call attention to the obvious difficulty of localizing the effects so produced. Brandenburg and Hoffmann²⁶ have attempted the isolation of the nodal region by means of cold. They state that when this region is thus isolated there is always a sudden change in the rate and sequence of the heart beat. Their article is, however, full of statements which can scarcely be reconciled with their conclusions. For instance, they state that injury to the auricles may cause other parts of the auricles to become the pace-maker. One is inclined to ask the question: Does this not provide them with a means of accounting for exceptions to the rule? It is for the purpose of avoiding injury to the auricles that they use cold to isolate the various regions of the auricles; despite this fact, they find that if the sinus node be isolated on three sides of a quadrangle by means of cuts, cooling of the node still causes the changes in rate mentioned above. Why, one might ask, do not the parts of the auricle injured by the cuts in this case now determine the beat of the heart?

²² Flack: Arch. Internat. de Physiol., 1911, xi, 111.

²³ Jäger: Deutsch. Arch. f. klin. Med., 1910, c, 1.

²⁴ Magnus-Alsleben: Arch. f. exper. Pathol. u. Pharmakol., 1911, lxiv, 228.

²⁵ Lohmann: Arch. f. d. ges. Physiol., 1908, cxxiii, 628.

²⁶ Brandenburg and Hoffmann: Med. Klin., 1912, viii, 16.

Quite recently Cohn and Kessel,²⁷ working with the perfused dog's heart, stated in a preliminary note that the last of four cuts removing a rectangular area containing the sinus node always causes stoppage with subsequent slowing, or at least subsequent slowing of the auricles, which never regain their former rapidity; that when the excision of the node is incomplete no change in rate results. They consequently conclude that the node is the pace-maker of the heart. In view of the obvious differences between these results and those obtained by myself working with Blackman, the experiments of Cohn and Kessel were repeated with certain modifications by Moorhouse.¹⁹ Moorhouse studied the reaction of the perfused dog's heart after excision of two rectangular strips, one (*a*) containing the sinus node, the other (*b*) immediately below this, but still a part of the sinus reunions. Fifty experiments in all were made, all with the greatest of care and with exacting controls. Inasmuch as the results obtained were almost identical in the case of strips (*a*) and (*b*), the conclusion was reached that there is a balance of rhythmical power through the caval portion of the sinus region. The nodal region is not more rhythmical than neighboring regions of the sinus reunions.

The final report of Cohn, Kessel and Mason²⁸ then appeared. It profoundly modified their preliminary statement, in that positive results, namely, stoppage and slowing of the auricles, were obtained in but 80 per cent to 90 per cent of the experiments. Notwithstanding these negative results they still are of the opinion that their experiments prove the sinus node to be the pace-maker of the heart. In view, however, of the fact that exactly the same results are obtained and just as frequently when a square of tissue below the sinus node is excised as when a square of tissue containing the sinus node is excised, experiments of this kind cannot be said to prove the specificity of the sinus node in the matter of impulse initiation.

²⁷ Cohn and Kessel: The Archives Int. Med., 1911, vii, 226.

²⁸ Cohn, Kessel and Mason: Heart, 1912, iii, 311.

EVIDENCE FROM WARMING AND COOLING

Another method that has been used for the purpose of locating the pace-maker of the heart has been to determine the area, warming or cooling of which will alter the rate of the whole normally beating heart. This method was first employed in the study of the mammalian heart by McWilliam,¹⁴ in 1888. McWilliam states that "the application of slight heat locally to the terminal part of the vena cava superior gives a very marked acceleration in the rhythm of the whole heart. A similar slight local heating of the ventricular apex or any part of the ventricular substance gives no change in cardiac rate." No further details are given, so that the reader is left to infer whether or not McWilliam tested the effect of temperature on other parts of the auricles than the superior vena cava. However this may be, McWilliam's final conclusion is that in the cat and the dog the usual site of origin of contraction is in the venous wall. In 1905, Adam,²⁰ working in Langendorff's laboratory, reinvestigated this subject and found that localized moderate warming and cooling altered the heart rate only in an area lying between the mouth of the two cavae and extending in the form of a triangle to the base of the auricle. The most sensitive spot lay between the two veins, somewhat nearer to the lower. Now, after the discovery of the sinus node, the same method in the hands of Ganter and Zahn²⁰ reveals that the nodal region, as delimited by Koch, alone is sensitive to temperature changes, the region overlying the thickest part of the node being the most sensitive spot. Brandenburg and Hoffmann²⁶ have obtained practically the same results. Ganter and Zahn and Brandenburg and Hoffmann, of course, conclude that the node is the normal pace-maker. The former investigators suggest a curious hypothesis to account for their observation that one part of the node may be more sensitive than others. It is obvious, therefore, that the method of warming and cooling

¹⁴ Adam: Pflüger's Arch. f. d. ges. Physiol., 1906, cxi, 607.

²⁰ Ganter and Zahn: Pflüger's Arch. f. d. ges. Physiol., 1912, exlv, 335.

also gives results that seem inconstant. By it the rate of the heart may be affected over the terminal portion of the superior cava, over the node and near the inferior cava. The results are, however, consistent in this respect, namely, that they have been obtained only within the limits of the sinus reunions. Those who have employed the temperature method have overlooked one consideration which may prove to be of considerable importance, namely, the accessibility of the region of the sinus reunions to the thermodes employed. Both His and Keith and Flack⁷ explicitly state, it will be recalled, that in the mammalian heart nearly all of the sinus recedes from the surface of the heart. To say the least, it is a rather remarkable coincidence that in the hands of recent investigators only the two regions that presumably remain at the surface of the auricles are affected by moderate temperature changes.

EVIDENCE FROM ELECTROCARDIOGRAPHIC STUDIES

Lewis⁸¹ has recently shown that the action current of beats of the auricles of the dog's heart, determined by electrical stimulation of various points on the surface of the auricles, resembles in form the normal action current only when the point stimulated is in the vicinity of the sinus node. This observation is considered as almost final proof that the impulse normally starts from the sinus node. The interpretation of Lewis' results, however, is not as simple as it may seem. It is necessary to bear in mind, for instance, that possibly this is one of the regions where primitive sinus tissue appears on the surface of the auricles. Is it not also possible that the impulse is so conducted through the auricle, owing either to the existence of definite paths, or to the thickness of the tissue, which in the region of the sinus node is comparatively great, that the sinus node region becomes negative electrically before other parts of the auricles? But there is still another possibility which an analysis of Lewis' results seems almost to substantiate.

The discussion of this possibility is begun with the assumption

⁸¹ Lewis: Heart, 1910-11, ii, 23.

that the impulse which causes the heart to beat starts in the sinus venosus and crosses the sino-auricular junction into the auricles at the most accessible point. Reference to the diagram (Fig. 2) shows that this point is just about where the sinus node lies. Now the amplitude of electrical changes associated with activity is largely dependent on the mass of tissue reacting. The sinus venosus in the cold-blooded heart is relatively large, yet even when the electrodes are placed directly on it the deflection shown by the string galvanometer is relatively small. Samoiloff,³² for instance, does not seem to picture a sinus action current in his extensive study of the frog's heart. The sinus of the mammalian heart probably contains much less tissue relatively than that of the cold-blooded heart. The action current of the former should consequently be correspondingly smaller. It is, therefore, not surprising that as yet no one has obtained a wave on the electrocardiogram of warm-blooded animals assignable to activity of the sinus.

Bearing in mind these assumptions an analysis of Lewis' results reveals the following: In all cases in which the contraction was evoked by a stimulus placed immediately over the sino-auricular junction (sinus node) or anywhere on the superior vena cava side of it, the *P* wave obtained, that is, the wave of auricular activity, closely approximates the *P* wave of the normal heart beat. In other words the curve is normal when it is started at the place where the impulse normally enters the auricle, or at some point on the sinus above this place. It is abnormal when it is started on the auricle or possibly on the sinus below the point at which it normally enters the heart. Lewis' experiments indicate, therefore, that the impulses pass into the auricle by way of the sino-auricular junction; they do not force us to the conclusion that the sinus node is the pacemaker.

The foregoing discussion also might serve to account for the observation of Lewis, Oppenheimer and Oppenheimer,³³ and

³² Samoiloff: *Pflüger's Arch. f. d. ges. Physiol.*, 1910, cxxxv, 417.

³³ Lewis, Oppenheimer and Oppenheimer: *Heart*, 1910-11, ii, 147.

of Wybauw,³⁴ that as a rule the point on the auricle first to become electronegative lies approximately over the region of the sinus node. For if the tissue of the sinus is small in amount, and for the most part submerged in the surrounding tissue, the point first to become negative would be the place where the impulse passes from the sinus into the auricle. It should also be mentioned that the points of primary negativity, as determined in these two investigations, do not exactly coincide. Furthermore, both record exceptions to the rule. These exceptions the authors consider of no significance. Yet to us it is obvious that if the sinus node has the specific function of starting the beat of the heart it should be possible to show that under normal circumstances it invariably performs this function. This the electrocardiographic studies have failed to demonstrate.

SIGNIFICANCE OF NODAL RHYTHM

We have thus far purposely omitted the discussion of a result very commonly obtained in experiments on the sinus regions of the auricles, namely, a change in the sequence of the auricular and ventricular beats. This change consists in a shortening of the auriculoventricular interval, or, more usually, in the actual disappearance of this interval, the auricles and ventricles contracting at almost exactly the same moment. The term nodal rhythm has been applied to this type of beat. It may appear suddenly or, occasionally, gradually after operations on the sinus region of the heart. It is assumed by those who consider the nodes of Keith and Flack and of Tawara the most highly rhythmical regions of the heart, that the synchronous a-v beat is the result of the usurpation by the auricular node of the function of setting the pace of the heart when the more highly rhythmical sinus node is excised. Inasmuch as the tissue of the auricular node resembles somewhat that of the sinus node, this change in the character of the beat is considered clear proof of the specialization of the so-called nodal

³⁴ Wybauw: Arch. Internat. de physiol., 1910, x, 78.

tissue in the direction of rhythmicity. The argument leading to this conclusion, it will be seen, is based on two propositions, namely, first, that the removal of the sinus node always results in the transfer of impulse initiation to the auricular node, and, second, that during the so-called nodal rhythm the impulse starts in the auricular node. Neither of these propositions has as yet been proved. The first proposition is by no means a fact.

It is true that extensive removal of auricular tissue, such, for example, as the liberal excision of much of the tissue in the sinus region in the perfused heart ¹² very frequently is followed by synchronous contractions of the auricles and ventricles. But simple excision of the sinus node alone rarely results in the appearance of nodal rhythm, and even when it does occur it may be only transitory, the normal or almost normal sequence often returning after a longer or shorter period of nodal rhythm. Nodal rhythm was but rarely seen in the experiments of Jaeger, Flack, Magnus-Alsleben, Cohn and Kessel, Moorhouse, and others. On the other hand, it is claimed that the abolition of the functional activity of the region of the sinus node by means of cold almost invariably produces nodal rhythm. One cannot help but feel, however, that the temperature effects were not as nicely localized as it is believed they were. Be that as it may, a perusal of the reports of these experiments shows clearly that removal of the sinus node by cold does not always result in nodal rhythm. Thus Ganter and Zahn ²⁰ state that "after stopping the activity of the sinus node by means of cold the auricles and ventricles do not always beat exactly synchronously. The as-vs interval may have a positive or negative value. While Brandenburg and Hoffmann ²⁶ state that occasionally after removing the sinus node by cold or by excision the synchronous beats of the auricles and ventricles may be transitory, and that the original normal sequence may again return.

But even if it be admitted for the purpose of argument that the auricular node is determining the beat of the chambers while they are beating synchronously, it would by no means follow that the auricular node normally is more rhythmical than all the rest of the supraventricular parts with the exception of the sinus

node. Might not the nodal rhythm be due to a temporary loss of the reactivity of the whole of the auricles, temporary inhibition, if that term is preferred, resulting from the tampering with the auricles, and that until the auricles recover, the auricular node, or, better, the next lower heart segment, determines the heart beat? It may be added that with the return of the normal sequence it can be shown that the auricles are setting the pace, since further operations on the auricles, such as cutting³⁵ or cooling the region of the coronary sinus³⁶ may again change the sequence. It is not entirely irrelevant to add, in this connection, that auricular strips containing the auricular node are not nearly so rhythmical as strips made from other parts of the auricle not alone while the sequence is normal, but even when, as a result of the excision of the great veins, the chambers are beating synchronously. Thus a companion strip from the coronary sinus region made at such a time always beats faster than the strip containing the auricular node.

Neither has it been proved that during so-called nodal rhythm the auricular node is invariably setting the pace of the heart. Indeed, almost the only observation in favor of this view is the fact that the chambers beat approximately simultaneously,³⁶ whereas there is just as good evidence to show that at such times the sinus may still be setting the pace of the whole heart. It has just been mentioned that extensive excision of the region of the great veins in the perfused rabbit's heart often results in so-called nodal rhythm. In ten consecutive experiments in which this occurred the auriculoventricular bundle was cut with a pair of scissors. The scissors were inserted through the opening made by the excision of the veins, one blade on either side of the exposed auricular septum down into the ventricles. A cut thus made in a heart as small as the rabbit's must undoubtedly have injured the node of Tawara. Yet this cut never slowed the auricles, indeed, it usually left

³⁵ Zahn: *Zentralbl. f. Physiol.*, 1912, xxvi, 495.

³⁶ Brandenburg and Hoffmann and Ganter and Zahn state that cooling or warming the auricular node after excision of the sinus node changes the rate of the beat.

their rate entirely unchanged; the ventricles on the other hand showed the slowing that usually follows section of the bundle of His. Be this as it may, there is no necessity for limiting explanations of the so-called nodal rhythm to the view that it can be produced only by impulses arising in the auricular node. Indeed, inspection of the progress of the contraction wave in cooled hearts, at a time when as a result of liberal excision of the great veins the auricles and ventricles are beating synchronously, has frequently revealed another cause. It can be seen in such experiments that the contraction wave may start in the region of the coronary sinus, and travel so slowly through the neighboring tissues of the auricles that the distant auricular appendices contract quite as late as the ventricles. Reference to Fig. 2 indicates clearly how a cut of this kind, by forcing the impulse to travel for a long distance through the auricular canal before it can gain access to the auricles, might lengthen the sino-auricular pause and so cause it to approximate the auriculoventricular pause.

Another question suggests itself here, namely, if it is admitted that the only two parts of the auricles that have sufficiently high rates of rhythm to dominate the rhythm of the auricles are the sinus node and the auricular node, how is the fact to be explained that the change from the auricular type of beat to the auriculoventricular type is frequently gradual, the auriculoventricular pause shortening slowly until the two chambers finally beat together?

STOPPAGE FROM INCISION OF THE NODE

Finally, a word with regard to the significance of stoppage of the heart from incision of the node. In 1907, Hering ⁵⁷ stated that a simple incision in the sulcus terminalis, which presumably involved the sinus node, stopped completely the beat of the supraventricular parts. This result was at once hailed by Keith and Flack as proof of their suggestion that the sinus node is the pace-maker of the heart. In the same year ¹² atten-

⁵⁷ Hering: *Pflüger's Arch. f. d. ges. Physiol.*, 1907, exvi, 143.

tion was called to the fact that stoppage of the heart often follows operations on, or sometimes even a mere touch anywhere on a rather large area of the auricles, and the view was then expressed that stoppage probably occurs only when the part stimulated is at the time determining the beat of the heart. Irrespective of what may be the fate of this suggestion, it is interesting to note that recent work ³⁸ has completely failed to confirm Hering. Incision of the node in the perfused heart of the dog does not stop the heart; on the contrary, it accelerates the heart rate.

II. LOCALIZATION OF CONDUCTIVITY IN THE HEART

HISTORICAL

In the historical introduction to the first part of this paper reference was made to the earliest hypotheses that were advanced to account for the sequence of the auricles and ventricles. We will, therefore, confine our attention here to the development of our modern ideas with regard to the dependence of the ventricles on the auricles. It has been said that Kürschner, in 1850, suggested a very complex explanation of the dependence of the ventricles on the auricles. One part of this explanation is of more than passing interest with reference to the topic in hand. "It is," Kürschner says, "now generally assumed that the musculature of the auricles is completely separated from that of the ventricles. From a study of the tissue composing the valves, I encountered conditions which are opposed to this view; I found muscle fibres extending from the auricle over into the valves." In attempting to account for the sequence of the heart beat he then proceeds to say:

The anatomical conditions of the heart are indeed such that a measurable interval of time can elapse between the contraction of the auricles and that of the ventricles. The muscle fibres which pass from the auricle into the venous valves contain the organic basis of this phenomenon. . . . They cannot contract without supplying a stimulus to the ventricles. The contraction of the auricles must, therefore, determine the contraction of the ventricles.

³⁸ See, for instance, Cohn, Kessel and Mason.

Obviously, Kürschner might be said to have been the first investigator to have shown that "the musculature of the auricles is not completely separated from that of the ventricles." There are, however, two all-important differences between Kürschner's point of view and the accepted point of view of today. Although the valve musculature is described by Kürschner as extending over the auriculoventricular junction, it is not in the location of the connecting muscle band, as we now know it, nor does the valve musculature fuse with the musculature of the ventricles.

Over a quarter of a century later, in 1876, we find recorded what has developed into the second claim to the demonstration of the crossing of the musculature of the auricles into the ventricles. In that year Paladino³⁹ wrote as follows:

The muscle layer of the sinus or auricle where it reaches the level of the auriculoventricular orifice loses the external circular layer of fibres, which stop, and is continued by the longitudinal fibres and the middle circular fibres downward to the interior of the valve leaflets . . . Of these fibres, the longitudinal terminate in the tendons of the second and third order . . . *And some tendons pass directly upon the walls of the ventricles*, where, by means of flattened muscle bundles, which are inserted upon the valve leaflets, *they break up into small tendons*.

In 1910, Paladino, on the basis of passages similar to the one quoted above, pleads to have his name connected with that of the discoverer of the auriculoventricular bundle, as having demonstrated a muscular connection between the auricles and ventricles. As a matter of fact, a few authors have actually heeded this plea. It is obvious, however, that the criticism we have applied to Kürschner's work applies with equal force to the work of Paladino;^{39, 17} no discrete definitely localized bundle is described, but rather scattered bundles in the valves, and there is no fusion of muscle bundles with the musculature of the ventricles.

In 1892-3, there appeared two articles by Kent,⁴⁰ which

³⁹ Paladino: *Arch. ital. d. biol.*, 1910, liii, 47.

⁴⁰ Kent: *Proc. Physiol. Soc.*, Nov. 12, 1892, and *Jour. of Physiol.*, 1893, xiv, 233.

seem to represent the first of the recent attempts to determine whether or not the musculature of the auricles and of the ventricles are completely separated by connective tissue. Owing to the existence of some difference of opinion as to the exact significance of Kent's work in the development of this subject,⁴¹ his results will be given as nearly as possible in his own words. In the adult animal (rat) a ". . . connecting sheet of muscle . . . is met with over a considerable area of the a-v groove; thus it may be mentioned that frequently in a single coronal section the connection may be seen between the outer (left) wall of the left ventricle and the left auricle, between the septum ventriculorum and the auricle, and between the right wall of the right ventricle and the right auricle." Describing a coronal section passing through the *junction of the left auricle with the left ventricle* of the heart of the newly-born rat, Kent says:

. . . at about the centre of the isthmus "the auricular fibres are seen to sweep freely down into the substance of the ventricular wall." "In the young rabbit of two days old . . . auricular fibres are seen sweeping down to the outer side of the fibrous ring, and become continuous with bundles belonging to the ventricular system. The connection also exists on the right side of the heart . . . and also in the septum to the right side of the ring bearing the mitral valve." In the monkey "the fibrous ring has attained a very perfect development and it is only here and there that places can be found to show the passage of muscular fibres across the groove."

ANATOMY OF THE AURICULOVENTRICULAR BUNDLE

In 1893, His called attention to the existence in the heart of a number of mammals of a single muscle bundle located in the posterior part of the septum and extending across the auriculoventricular junction obliquely from above and behind,

⁴¹ Meltzer: Med. Rec., New York, 1909, May 2, p. 873; also Nov. 27, p. 914.

"It should be noted that the term "isthmus" as used here could not and was not by Kent intended to be synonymous with septum, since the section is from the junction of the left auricle with the left ventricle. Compare with Meltzer, loc. cit., note 41.

downward and forward. In a review written in 1899, His¹⁶ correctly refers to the bearing of Kent's work on his in the following terms:

In man, indeed in mammals in general, a layer of connective tissue grows in between the muscle walls of the ventricles and auricles and separates these parts almost completely. Nevertheless muscle fibres have been found in this layer (Stanley Kent) and I myself have demonstrated a bundle present in mammals as well as in man, which passes from the posterior wall of the right auricle down to the ventricular septum.

While the existence of this single bundle, now usually and correctly designated the bundle of His,¹⁷ has since been abundantly confirmed, the more recent work by Humblet, Retzer, Breaunig, Tawara, and others, has added much to His' original description. Much more, although not enough yet, is now known of its origin in the auricles, of its mode of determination in the ventricles and of the histology of its various parts. Overlooking for the present certain details on which opinion is as yet divided, the system connecting the auricles with the ventricles may be described briefly as follows:

It begins in the auricle in the posterior part of the septum, just above the auriculoventricular junction, and just anterior to and in the floor of the coronary sinus. Thence it courses to the auricular node. Some authors describe a very close connection between the node and the auricular tissue. According to Cohn,¹⁸ for example, it would seem that there is a general transition of auricular fibres into the characteristic nodal fibres. The number of fibres forming the connection, however, varies. "There may be a great many, closely packed together, the strands separated by masses of connective tissue; or there may be but a few rather thinner fibres with only delicate connective tissue strands between." The node of Tawara, into which these strands flow, is composed of characteristic branching and anastomosing cells which possibly were seen by Kent. Beyond the node the bundle, now compact and slender and taking on the

¹⁶ His: *Deutsch. Arch. f. klin. Med.*, 1899, **lxiv**, 316.

¹⁷ Cohn: *Heart*, 1909-10, **i**, 172.

characteristics of Purkinje cells, crosses the auriculoventricular junction and, continuing its course downward and forward, comes to lie on the upper edge of the muscular septum of the ventricles where it joins with the membranous part. The subsequent course of the conducting system is probably familiar to all. It can be best and indeed strikingly demonstrated by means of the injection method of Lhamon.⁴⁶ Lhamon has shown that when a colored injection fluid is forced through a hypodermic needle into the conducting system it will, owing to the connective tissue sheath, remain in that system and flow even into its ultimate branches. It is thus possible to make very evident the division of the main bundle into two limbs, a right and a left, the subendocardial course of these limbs down the respective sides of the ventricular septum, their branching into secondary twigs, some of which pass by way of the false tendons across the cavities of the ventricles to the papillary muscles, and their further branching into an anastomosing network, the ultimate fasciculi of which dip down into the myocardium, and gradually change into fibres of the ventricular type, the individual fibres eventually terminating in a most interesting way in the conical point of a fasciculus of heart muscle.

Comparative anatomy and embryology, too, have added much to the significance of the His-Tawara system. Keith and Flack, in 1907, showed that in the simplest form of vertebrate heart a portion of the auricular canal, that part of the heart which in primitive forms joins the sinus with the ventricle, extends down into, or is invaginated into the ventricles. This invaginated part forms an isolated layer beneath the auriculoventricular valves. It is assumed in the primitive mammalian heart that complete muscular connection between the auricles and ventricles exists around the whole auriculoventricular junction. As we ascend the animal scale, however, the invaginated portion of the auricular canal is encroached on more and more by the growth of connective tissue, until there is left only a small part of this musculature; it forms the auriculoventricular

⁴⁶ Lhamon: *Am. Jour. Anat.*, 1912, xiii, 55.

bundle. However, in certain animals, the rat, for example, auricular and ventricular fibres appear to come into close apposition in other places, especially in the right lateral auriculoventricular region. This, Keith and Flack venture to suggest, represents "one of the connections described by Stanley Kent. This close apposition, however, cannot be looked on as a connection; the auriculoventricular bundle is to be regarded as the sole connection between the auricular canal and the ventricle."

Mall⁴⁶ has studied the development of the auriculoventricular bundle in human embryos. At very early stages (embryo 3.9 mm.) the auricular canal forms a complete muscular connection between the sinus and the ventricle. Soon, however, as the result of the formation of subendocardial cushions of connective tissue, this ring becomes separated into a number of bundles, amongst which can be recognized at this time one occupying the same position and course as the auriculoventricular bundle in the adult. "The additional strips," Mall says, "may be of significance in view of Romberg's and Kent's observation." Kent found such bundles in the left wall of the heart as well as in the right wall in rats and rabbits. It is possible that some of these strips may be constant, or they may be variations. "At any rate," he goes on to say, "their presence has not been established as has the atrioventricular bundle of His." The auriculoventricular bundle, consequently, is not a structure of recent development; rather, it is a part of the wall of the primitive tube from which the heart is evolved. This fact, as has been said, should have some weight in inferring the function of the bundle from its structure; despite the great changes in, and the apparent complication of, the adult mammalian heart, it still preserves its primitive arrangement.

PHYSIOLOGY OF THE AURICULOVENTRICULAR BUNDLE

Considering now the physiological aspects of the problem of localizing conduction from auricles to ventricles in the warm-

⁴⁶ Mall: Am. Jour. Anat., 1912, xiii, 284.

blooded heart, the view which previous to 1893 held practically universal sway was that the correlation of the work of the auricles and ventricles was affected through nerves crossing the auriculoventricular junction. An excellent idea of the point of view held by the physiologists of this period may be conveyed by a quotation from an article by Tigerstedt⁴⁷ in which are recorded the results of severing completely by means of a cut the connection of the auricles with the ventricles in the rabbit's heart. In order to make this quotation clear, it should be preceded by the statement that in the previous year Wooldridge⁴⁸ had accomplished the same separation by means of a mass ligature, with the result that the auricles and ventricles contracted independently of each other. Tigerstedt says:

Wooldridge in dogs and cats performed the experiment of severing the *nervous connection* [my italics] between the auricles and ventricles, that is to say he made the Stannius experiment on the warm-blooded heart.

And again, by way of introduction to his experiments Tigerstedt says: The interesting results obtained by Wooldridge by means of his ligature made it necessary to repeat with more rigorous methods the separation of the *nervous connections* [my italics] between the ventricles and auricles because it might be objected that the ligature failed to divide all of the nerve fibres between the auricles and ventricles . . .

This assumption seemed justifiable in view of the prevailing opinion that there was no muscular connection between the auricles and ventricles.

In the same paper in which Kent described muscular connections in various parts of the auriculoventricular junction, mention is made of some experiments in which a clamp was applied to the auriculoventricular groove of the mammalian heart just as Gaskell had done in the frog's heart. Kent states without giving the records "that almost precisely similar results [to those of Gaskell] were obtained." It may, therefore, be assumed that he obtained with this clamp the various

⁴⁷ Tigerstedt: Arch. f. Physiol., 1884, p. 497.

⁴⁸ Wooldridge: Arch. f. Physiol., 1883, p. 522.

stages of partial and complete block. The experiments of Wooldridge, Tigerstedt and Kent, therefore, demonstrate conclusively that in the mammalian heart the impulse which causes the ventricles to beat arises in the auricles and crosses the auriculoventricular junction; the old view that the sequence is due to stimulation by the blood is disproved. Shortly after His⁴⁹ described the muscular bundle that bears his name, he read before the Physiological Congress a paper describing the results of cutting this bundle. No final report of these experiments has ever appeared, and it was not until the bundle of His was redescribed in 1904 by Retzer, by Breaunig and by Humblet that the attention of physiologists was attracted to this structure. Then Humblet⁵⁰ showed, as had been shown by His, that section of practically nothing but the bundle in the perfused heart results in complete dissociation of the auricles and ventricles. A year later the same observation was made by Hering,⁵¹ also in the perfused heart. Simultaneously the results were published of compressing in a specially devised clamp practically nothing but the His bundle in the heart *in situ*.⁵² The results thus obtained were similar to those following compression in a clamp of all of the auriculoventricular junction in both cold- and warm-blooded animals. These results have since been abundantly confirmed. Practically the only conflicting evidence comes from the Bern laboratory. Lomakina⁵³ says that dissociation of the auricles and ventricles can be obtained by dividing the superficial macroscopic nerves in the auriculoventricular groove. This result has not been confirmed. Paukul⁵⁴ and Kronecker⁵⁵ state that crushing the auriculoventricular bundle in rabbits does not

⁴⁹ His: *Zentralbl. f. Physiol.*, 1895, ix, 469.

⁵⁰ Humblet: *Arch. Internat. d. Physiol.*, 1904, c, 278.

⁵¹ Hering: *Pflüger's Arch. f. d. ges. Physiol.*, 1905, evii, 97.

⁵² Erlanger: *Zentralbl. f. Physiol.*, 1905, xix, 9; also *Jour. Exper. Med.*, 1906, viii, 8.

⁵³ Lomakina: *Ztschr. f. Physiol.*, 1900, xxxix, 377.

⁵⁴ Paukul: *Ztschr. f. Physiol.*, 1908, li, 177.

⁵⁵ Kronecker: *Brit. Med. Jour.*, 1910, i, 135.

block the passage of the impulse into the ventricles. Cohn and Trendelenburg⁵⁶ have offered what seems to be a plausible explanation of this anomalous result. They have found that in the rabbit the bundle may not pass into the ventricle as a single strand, but may divide into several strands which spread out after the fashion of a fan. They suggest that some of these branches probably escaped inclusion in the ligature as placed by Paukul and Kronecker. We are, therefore, justified in asserting that experiments of the kind thus far described prove that the only *functional* connection between the auricles and ventricles is by way of the His bundle.

It is not, however, unreasonable to maintain that other connections exist, such, for example, as were described by Kent, that under ordinary circumstances such other connections are dormant, and that in the course of the few hours the heart is under observation in experiments as ordinarily performed these connections cannot develop their activity sufficiently to perform vicariously the function of the His bundle. This objection seems to be met by those instances of chronic heart-block in man, in which a lesion, more or less accurately limited to the region of the auriculoventricular bundle, undoubtedly has served to block permanently the passage of the excitation wave through the auriculoventricular junction. Nevertheless, clinical observations, even when confirmed by post-mortem findings, do not carry the conviction of a clean-cut experiment; there is always the possibility that tissues other than those found to be diseased may be the seat of pathological processes, which, however, have escaped detection. This objection has been removed by some experiments in which heart-block was produced by crushing under aseptic precautions the auriculoventricular bundle in the clamp above alluded to and then allowing the animals (dogs) to live.⁵⁷ Two of these animals survived the operation 320 and 343 days, respectively. During this entire period there was complete dissociation of the auricles and ven-

⁵⁶ Cohn and Trendelenburg: *Pflüger's Arch. f. d. ges. Physiol.*, 1910, cxxxii, 1.

⁵⁷ Erlanger and Blackman: *Heart*, 1910, i, 177.

tricles. We may conclude, therefore, that there is no connection between the auricles and ventricles that can vicariously assume the functions of the bundle of His. Thus the path of conduction across the auriculoventricular groove is narrowed down to the auriculoventricular bundle.

Now that we know that the auriculoventricular bundle is as much a part of the primitive heart tube as any other part of the heart, we could scarcely expect conduction in it to differ from conduction in the rest of the heart, the presence in the bundle of a considerable amount of nerve tissue to the contrary notwithstanding.⁵⁸ Nevertheless, the question has been asked, Is it possible to carry further the localization of impulse conduction in this region by determining whether it is through muscle or through nerve? The results of experimentation in this direction, although suggestive, are still far from being conclusive. The fact that in animals regeneration of function does not occur even in the course of a year after complete section of the auriculoventricular bundle, would seem to indicate that nerves are not concerned with the process of impulse conduction. This conclusion is based on the usually accepted view with regard to the power of regeneration of heart muscle and of nerve. Wounds of heart muscle heal by the formation of scar tissue; the muscle cells show little, if any, tendency to regenerate.⁵⁹ On the other hand, it is well known that in due time nerves will regenerate. This is true not alone of nerve trunks, but also of nerve plexuses, such, for example, as the myenteric plexus.⁶⁰

When our attention was first directed to this subject a perusal of the literature revealed that regeneration of nerve and of muscle, in so far as it pertains to the heart, had been studied by histological methods only. So far as could be ascertained, no effort had been made to determine whether restoration of conductivity across a healed wound of the heart will occur. Consequently the attempt was made to determine

⁵⁸ Wilson: Anat. Rec., 1909, viii, 262.

⁵⁹ See Thorel: Lubarsch and Ostertag's Ergebnisse, 1903, ix, 861.

⁶⁰ Meek: Am. Jour. Physiol., 1910, xxv, 367.

whether a functional connection between the auricles and ventricles could be established by uniting contiguous surfaces of the auricles and ventricles, which have been denuded of their epicardial covering. This attempt failed. It was not, however, considered conclusive because of the great difficulty of obtaining close apposition of thin-walled auricle to ventricle. For the purpose of putting this question of regeneration to a crucial test, the following experiment was then made:⁶¹

Under aseptic precautions the tip of the auricular appendix of the dog's heart was crushed in a clamp so as to sever it functionally from the auricle proper excepting a narrow strip along one edge. The tip was not completely isolated, since it was feared that then atrophy of the functionless part would occur and would interfere with the interpretation of the results. The animal was then allowed to live some 130 days. Then the tissue of the auricle was crushed in a line extending out to the tip of the auricle and intersecting at right angles the old line of crush. By this procedure the appendix is divided into two triangular areas, one separated from the heart by the old and new lines of crush, the other still functionally connected with the heart through the undestroyed isthmus at the edge of the auricle. By using the second area as a control, it was then found that functional connection between the first area and the heart had not developed. Histological examination revealed that heart muscle had not grown across the old contusion, whereas nerve could be traced from one side to the other. The presence of this nervous union obviously did not suffice for the conduction of the impulse.

Such a result makes it very probable, although it does not prove, that the muscular rather than the nervous elements of the His bundle carry the impulse from the auricles to the ventricles. In support of this conclusion it might be added that Cullis and Dixon⁶² have shown that the application of a 5 per cent. solution of cocaine to the bundle of His does not produce heart-block, although all of the nerve fibres with which the cocaine comes into contact would certainly be paralyzed.

We have yet to consider conduction within the ventricles. Is the impulse delivered by the His bundle to the ventricular

⁶¹ Erlanger: Am. Jour. Physiol., 1909, xxiv, 375.

⁶² Cullis and Dixon: Jour. Physiol., 1911, xlii, 156.

musculature at or near the point where it crosses the auriculo-ventricular junction, or must it first traverse the entire complicated system described by Tawara, DeWitt, Lhamon and others?

These questions were first formulated only a few years ago and are still the subject of discussion. The experiments devised to answer them are as yet but little beyond the formative stage. Considering first the results of cutting both of the main divisions of the bundle of His, the general statement may be made that the mass of evidence points to a union of the bundle fibres with the ventricular musculature below the bifurcation. Thus Barker and Hirschfelder⁶³ have shown in the dog that cutting the left branch usually gives complete block. In the one case in this series of experiments in which block did not appear, both the ventricles seemed to contract coördinately. Eppinger and Rothberger⁶⁴ state that cutting one limb produces an obvious effect at once; the two ventricles seem to alternate. Complete block, however, did not follow section of one limb, but only section of both. The difference in the results of these two investigations is probably merely one of degree. The experiments of Biggs, though, are not in harmony with either of the foregoing researches. Biggs⁶⁵ finds that in the rabbit, section of all branches of the bundle of His does not cause heart block, and he furthermore finds, as do also Cullis and Dixon, working with the same animal, that retrograde conduction may sometimes occur after section of the bundle. This result leads one to suspect either that these investigators failed to cut all of the branches of the bundle, despite the fact that both seem to have been aware of the variations that occur in the bundle of the rabbit's heart, or that the auricles were stimulated mechanically by the ventricles, as Cullis and Dixon seem inclined to believe. So far as present purposes are concerned

⁶³ Barker and Hirschfelder: *The Archives Int. Med.*, 1909, iv, 192.

⁶⁴ Eppinger and Rothberger: *Centralbl. f. Physiol.*, 1911, xxiv, 1055.

⁶⁵ Biggs: *Brit. Med. Jour.*, 1908, i, 1419.

the results, however, indicate that the termination of the His bundle lies some distance beyond its bifurcation.

How much farther on its course into the ventricles does the impulse remain in the conducting system? Tawara is of the opinion that the impulse is carried in the bundle to the most distant parts of the ventricles; indeed, to the papillary muscles first. The moment of contraction of the papillary muscles, it might therefore be suspected, should serve to throw some light on this question. Do they contract before, with or after the body of the ventricles? Until quite recently it was regarded as probable that the papillary muscles contract synchronously with or possibly a moment later than the body of the ventricles.⁶⁶ The reinvestigation of this subject that has been stimulated by the suggestions of the anatomists has as yet led only to conflicting results,⁶⁷ which need not be reviewed here.

It has thus far been assumed that the secondary branches of the His-Tawara system, which, as has been said, are composed of Purkinje tissue, carry the impulse through the ventricles. This assumption is based on anatomical observations and on the observation, to which reference has just been made, that section of the His bundle, or of its two main branches, produces heart block. In view of the possibility of misinterpreting the results so obtained, it was thought that it would be interesting to have some definite information with regard to conduction in the ventricular portion in the His-Tawara system. The first attempts in this direction seem to have been made by Hering.⁶⁸ He cut the auriculoventricular bundle in the dog and then stimulated the cut surface. More recently Cullis and Dixon applied electrodes directly over the intact bundle in the rabbit's heart. While the results obtained in both of these researches indicate that the bundle responds to direct stimulation, the very close proximity of the ventricular muscula-

⁶⁶ For a discussion of this subject see Shaefer's Text Book of Physiology, London, 1900, ii, 10.

⁶⁷ Saltzmann: Skand. Arch., 1908, xx, 233; Hering: Pflüger's Arch. f. d. ges. Physiol., 1909, exxvi, 225.

⁶⁸ Hering: Pflüger's Arch. f. d. ges. Physiol., 1910, cxxxii, 572.

ture, which could not have been more than 1 mm. away from the electrodes, renders the conclusions somewhat uncertain.

It has been said that some of the branches of the His-Tawara system cross the cavities of the ventricles by way of the false tendons or interventricular bands. The studies of Petersen, which were confirmatory of Miss DeWitt's observations, demonstrate that some of these interventricular bands in the beef's heart consist of Purkinje fibres and connective tissue exclusively. Thus the way was opened to a conclusive reply to the question of irritability and conductivity in the Purkinje system. It has been determined in the perfused beef's heart that stimulation of false tendons, which were found by subsequent histological examination to be entirely free of heart muscle proper and to contain as irritable structure only Purkinje tissue, causes a contraction of the ventricles.⁶⁹ There could be no question in these experiments of an escape of the current to the ventricular musculature, since often the electrodes were applied to the false tendons a centimeter or more from their insertion into the ventricular wall, while the strength of the stimulus eliciting a reply from the false tendon in many cases did not suffice to elicit a reply when applied directly to the ventricular wall.

This method has also served to shed some light on other important matters. By means of it, it has been found possible to show that impulses carried to the ventricles by way of the His-Tawara system are not of necessity delivered first to the papillary muscles. If a false tendon be divided near its middle and the two stumps be stimulated separately, the ventricles will, in both cases, contract. Assuming that in both cases the impulse is delivered to the papillary muscles, the distance it must travel by way of the papillary stump of the false tendon would be much shorter than the distance by way of the septal stump, and we should expect to find a corresponding difference in the latent period of the ventricular contraction. As a matter of

⁶⁹ Erlanger: *Am. Jour. Physiol.*, 1912, **xxx**, 395.

fact, however, the latencies have, as nearly as can be determined, the same duration.

However this may be, it can be shown that the central stump of the false tendon probably does not terminate close to its insertion into the septum. It is well known that practically all of the main branches of the His bundle lie immediately under the endocardium, the terminal branches alone apparently dipping into the depths of the myocardium. It, therefore, seems justifiable to assume that a cut a couple of millimeters deep circumscribing the septal insertion of a false tendon severs all of the Purkinje tissue connected therewith, excepting that of the terminal branches. Such a cut has been found to annul the response of the ventricles to stimulation of the circumscribed false tendon, while the mere ringing of an area of heart muscle does not of itself annul the irritability of the enclosed area. At least two interpretations of this result are possible: (1) Either the immediate connections of the false tendon with the subjacent heart tissue are not extensive enough to carry the impulse, that is to say, a relatively complete block results from the operation; or (2) the impulse before it is delivered to the myocardium must first be carried to some distant point by the large subendocardial strands of the conducting system. It remains for future work to settle this matter.

Another point of some interest in connection with the localization of conduction is the following: It is well known that impulses are conducted in either direction between the auricles and ventricles. Consequently it should be possible to show that the conducting system, if properly so-called, will carry impulses in either direction. Experiments with false tendons have shown not alone that this is the case, but also that the impulses are carried at the same rate in either direction.

CONCLUSION

The first conclusion one is apt to draw from a review of the work that has been done in the effort to localize the site of impulse initiation and conduction is that the former subject

at least is in a state of hopeless confusion. I venture to predict, however, that when the last word has been said, the structure and function of the mammalian heart will be found to be almost identical with the structure and function of the heart of cold-blooded animals, of which the heart of the eel, owing to its simplicity and to the care with which it has been studied, may serve as a type. The normal sequence of the eel's heart differs in no wise from that in other hearts, sinus, auricles and ventricles contracting in the order given, which is also the order of the rhythm of these parts when isolated. Under the eye it can be seen that the contraction begins in the venous part of the sinus. It passes from the sinus directly into the nearest part of the auricle and then spreads over the auricular tissue, whence it passes into the auricular canal through which it finally involves the central fibres of the ventricle. "The rhythmical power of each segment of the heart varies inversely as does the distance from the sinus." The auricular canal, which might almost be regarded as a prolongation of the sinus tissue, possesses a much higher rhythmical power than the auricles. Therefore, in the mammalian heart we should expect the rhythmicity of the sinoventricular bundle to be exceeded only by that of the sinus region, and this seems to be the case. In the eel's heart the impulse normally reaches the ventricle by way of the auricle, but it can reach the ventricle directly by way of the auricular canal also. In the latter event the auricles do not contract. The anatomical possibility of this path has been all but worked out in the mammalian heart. It is believed that the finding of such a path would help materially toward accounting for the appearance of nodal rhythm following excision of the upper part of the sinus region as well as for many other of the phenomena noted in this paper. In any event, we cannot afford, in the interpretation of the functions of the heart of man, to ignore the results of investigation in the field of comparative physiology.

STUDIES ON THE CIRCULATION IN MAN*

THE BLOOD FLOW IN THE HANDS AND FEET IN NORMAL AND
PATHOLOGICAL CASES

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FOR many purposes it is more important to know the rate at which the blood is flowing in an organ, the so-called mass movement of blood, than to know the pressure in the artery supplying the organ or part. The arterial pressure is not by itself a measure of the flow. With a high arterial pressure the flow may be small, with a low arterial pressure it may be large. For the rate of passage of the blood from arteries to veins obviously does not depend upon the arterial pressure alone, any more than the quantity of water which flows per minute along a pipe depends solely upon the height above the ground of the reservoir which feeds it. Two other factors of prime importance are concerned (the viscosity of the liquid itself being assumed to be constant): (a) the cross section of the pipe, (b) the height above the ground of the orifice from which the water escapes. (a) corresponds to the calibre of the vessels between artery and vein, (b) to the venous pressure.

At present we possess no method for measuring the blood flow which is at once simple enough and accurate enough for clinical purposes. I have accordingly worked out a method which permits the quantity of blood passing through a part like the hand to be easily determined with approximate accuracy. Changes produced in the flow by reflex vasomotor influences, especially those connected with changes in external temperature, by the application and withdrawal of a tourniquet or Bier's bandage, by alterations in the mechanics or chemistry of the

* Delivered November 23, 1912.



FIG. 1.—Hand calorimeter, for description see text (p. 87).



FIG. 2.—Arrangement for the measurement of handflow with the patient in the sitting position.

respiration, as in forced breathing or the inhalation of oxygen, and by muscular exercise, have also been investigated in this way in normal and clinical cases.

SECTION I. METHOD

The method depends upon the fact that the amount of heat produced by a part like the hand during rest is negligible in comparison with the heat conveyed to it by the arterial blood. If, then, we determine the amount of heat given off by the hand to a calorimeter in a given time, and know the temperature of the incoming (arterial) and of the outgoing (venous) blood, we can calculate how much blood must have passed through the hand in order that it might give off this amount of heat. The quantity of heat given off is estimated by putting the hand into a calorimeter such as is shown in Fig. 1.

It consists of an interior copper vessel containing a known amount of water (in the experiments usually about three litres), into which the hand is inserted through an orifice of appropriate size and shape in the lid, heat-tight closure being made by the collar of thick felt shown on the top of the calorimeter. The interior vessel is packed in broken cork in a larger outer vessel and the lid is covered with sheet cork to reduce as far as possible the loss of heat, and to protect the calorimeter against irregular cooling when exposed to draughts. The actual loss is estimated by separate experiments, and added to the amount of heat given off by the hand as indicated by the rise of temperature in the water. The hand is prepared for insertion into the calorimeter by a preliminary immersion, for not less than ten minutes, in a large bath containing water at approximately the same temperature as that in the calorimeter. The temperature of the water in the calorimeter is read on a thermometer permitting hundredths of degrees to be accurately estimated. The calorimeter is mounted on a stand which can be raised or lowered by a screw to permit its use either for a patient sitting in bed or for an ambulatory patient who is able to sit in the high chair shown in Fig. 2. As a general rule the flow in the two hands is simultaneously measured. The quantity of blood in grammes flowing through the hand in the time of the experiment is given by the formula:
$$Q = \frac{H}{T-T^1} \cdot \frac{1}{s}$$
 where Q is the quantity of blood, H the heat given off by the hand, T the temperature of the arterial blood, T^1 the temperature of the venous blood, and s the specific heat of blood. In estimating H the water equivalent of the hand itself (obtained by multiplying its volume by 0.8) and the water equivalent of the calorimeter (80 grammes) must be added to the

quantity of heat corresponding to the actually observed rise of temperature. The specific heat of blood is taken at 0.9. Knowing the volume of the hand, we can express the flow in grammes per minute per 100 c.c. of hand substance. The volume of the hand is easily estimated by the amount of water which it displaces, when immersed in a glass douche can to the level to which it was inserted into the calorimeter. The douche can is connected by the tubulure to a burette, on the scale of which the vertical displacement of the water is read off. The amount of water which must be added to that in the can in order to give the same level in the burette is clearly the volume of the hand. The distance to which the hand is to be inserted into the calorimeter is fixed by making a horizontal mark with a pencil at the level of the lower border of the styloid process of the ulna. A parallel mark is drawn above this at a distance equal to the combined thickness of the felt collar and the lid of the calorimeter, and this second mark is just kept in view above the collar during the experiment. The lower mark must then define the limit up to which the hand is enclosed in the calorimeter. The collar is supported by a flange around the orifice. The temperature of the arterial blood at the wrist is taken as 0.5° below the rectal temperature, since this was the difference actually found in a normal person. It can be measured by determining that temperature of the calorimeter at which the hand neither gains nor loses heat. Where the rectal temperature cannot be conveniently obtained the mouth temperature is taken as that of the arterial blood at the wrist. The temperature of the venous blood is taken as the average temperature of the calorimeter during the experiment, since direct estimations of the temperature of blood collected by puncture of hand veins, during immersion of the hand in baths at known temperatures, showed that the excess of the temperature of the venous blood over that of the bath was so small as to be negligible for such bath temperatures as are used in the experiments. All details of these observations are omitted here. It may be remarked that since no account has been taken of the small excess of temperature of the venous blood over that of the calorimeter which must necessarily exist even in the superficial veins, the results cannot be too large, but may, on the contrary, be somewhat below the true values. This is important because for nearly all purposes it is much more useful to know the minimum flow below which the true flow cannot lie than to know the possible maximum flow. Some of the blood leaves the hand by deep veins, but the dimensions of the part and the anatomical situation of the vessels make it certain that no great error can be introduced by taking the temperature of the blood in the superficial veins as the average temperature of the whole of the blood as it leaves the hand.

The method for the measurement of the flow in the hands¹ was modified to suit the feet. This made it possible to make observations on persons who were too ill to sit in a chair for hand flow measurements.

Since the heat given off per 100 cubic centimeters of tissue per minute by the foot of a normal adult is considerably less than that given off by the hand, it was necessary to construct the interior vessel so that as small an amount of water as possible would suffice to immerse the foot completely.

TECHNIC OF FOOT FLOW MEASUREMENTS

In its final form the foot calorimeter consists of an interior oval vessel of tinned copper (Fig. 3) packed in broken cork in an outer vessel of galvanized iron. Both vessels are somewhat wider at the anterior (toe) end than at the posterior end. The top of the inner vessel has in it an oval opening somewhat wider at the anterior end. This opening, as is obvious from the shape of the foot, must be much larger than in the case of the hand calorimeter, and when the foot has been inserted it is partly closed by the removable copper lid shown at the right lower corner of the figure. The hole in this lid allows it to be lifted easily by the fingers. On the lid, once the foot is in position, lies the thick felt collar shown at the left of the figure. Inside the calorimeter the foot rests on thick copper wire netting, shown leaning against the front of the calorimeter. This allows the water to pass freely under the foot when it is stirred by the two goose feathers, the ends of which are seen protruding from the two openings, one on each side of the thermometer. The calorimeter in the figure is tilted so as to display the posterior end of the footrest lying in position on the bottom of the inner vessel. The anterior part of the top of the inner vessel slants down somewhat toward the front in order to reduce the capacity of the vessel without encroaching on the space needed for the toes. The thermometer is protected against contact with the patient's toes by a cylinder of copper perforated with numerous holes, which passes down through the top of the inner vessel to the level of the lower end of the bulb. The orifice for the introduction of the foot is surrounded by a flange on which the lid and the felt collar rest. Vertical rings of copper surround all the orifices so as to allow the top of the inner vessel to be covered, first with a layer of broken cork,

¹ Stewart, G. N.: Heart, 1911, iii, 33.

and above that with sheet cork. The upper surface of the sheet cork is varnished.

Fig. 4 shows the position of the patient with his feet in the calorimeters when he is well enough to sit in the high chair employed in the measurement of the flow in the hand. For the convenience of the observer the chair and the calorimeters are placed upon a platform so as to elevate the thermometers to a sufficient height above the floor to enable them to be read conveniently. By a simple method of fixation all possibility of slipping of the chair is prevented.

In the first experiments a horizontal pencil mark was drawn around the ankle, always bearing the same relation to the external malleolus, and above this a parallel line was drawn at a distance equal to the thickness of the felt collar plus the thickness of the flange. The height of the calorimeters was then adjusted so that the upper line just appeared above the felt collar, the patient sitting in the chair with his legs hanging down. The footrest inside the calorimeter was not used with this arrangement. It was found to be somewhat troublesome for the patient to maintain the same level throughout the experiment in this way. It was therefore decided to abandon it and to cause the patient to set his foot on the footrest. Before withdrawal of the foot a pencil line is now traced around the ankle just below the flange, or it may be traced above the collar, and after withdrawal of the foot a parallel line traced at a distance below the first line equal to the combined thickness of collar and flange. The object of the first procedure was to insure that in all experiments the foot should be inserted into the calorimeter to the same anatomical level, as was always done with the hands. In the case of the hands undoubtedly a fairer comparison of the flow in different individuals is obtained in this way than if the fingers were made in every case to touch the bottom of the calorimeter, since the inclusion of different proportions of the wrist and forearm would to some extent vitiate the results. From the shape of the foot, however, it is clear that the second procedure leads to a much smaller variation in the portion of the foot immersed than would be the case for the hand, since in the adult the variation in the vertical distance from the sole to a given anatomical point on the ankle is much less than the variation of the length of the hand,—from the tip of the middle finger to a fixed anatomical point on the wrist, for example. As a matter of fact, in the adult patients examined the variation in the distance between the flange and a fixed point on the external malleolus when the sole rested on the footrest was small. Any error in comparing the feet of different persons was further reduced by the fact that the difference of level affected the portion of the foot (the ankle) whose horizontal cross section was smallest. For very



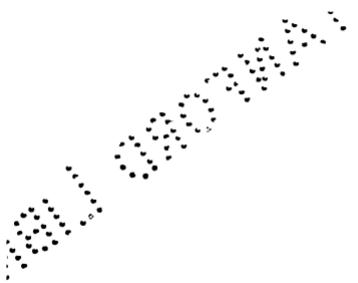
FIG. 3.—Foot calorimeter. For description see text (p. 89).



FIG. 4.—Arrangement for the measurement of foot flow with the patient in sitting position. At the left is shown the arrangement for measuring the volume of the feet. The legs should be more completely covered.



FIG. 5.—Arrangement for measuring the foot flow in a patient not well enough to sit up. The legs should be more completely covered than is indicated in the figure.



small feet, as those of children, an additional footrest which increased the space between the sole of the foot and the bottom of the calorimeter was employed. A great advantage of the footrest, in addition to the increased comfort of the patient, is the certainty that without any attention the foot remains at the same level within the calorimeter throughout the experiment. For particular purposes in the case of children or of adults with exceptionally small feet, it may sometimes be desirable, where accurate comparison is required with other cases, to revert to the first method, although, of course, for comparison of the flow in the feet of one and the same person at different times or under different conditions, this would offer no advantage.

The volume of the foot was measured by displacement in the same way as that of the hand. The oval copper vessel at the left of Fig. 4 was made for this purpose. The cross section of the vessel must be as small as possible in order to permit as large a change of level as possible in the attached burette. Where very large or very small feet are being investigated it is of advantage to have vessels of correspondingly different size.

When patients are not well enough to sit up in the chair the flow in the feet can be easily measured in the way shown in Fig. 5. The subject is lying on his back on a movable bed with his legs hanging over the foot of the bed. The height of the calorimeters is adjusted so that the soles of the feet rest on the footrest. No complaint of discomfort was made by any of the fever patients investigated in this way.

The technic of the preparatory bath is the same as that for the hands, except that instead of the patient putting his feet into the bath, the bath is generally slipped up over his feet. This is necessarily the case where patients are examined in bed. On account of the greater thickness of the feet, the period of immersion in the bath can advantageously be made longer than is necessary for the hands. For the same reason it is probable that the calculated results differ from the actual flow by a greater amount in the case of the feet than in the case of the hands. In both, of course, the observed flow establishes a minimum below which the actual flow cannot lie. It was pointed out in the previous communication that this follows from the principle of the method.

Another point of considerable importance is that the feet and legs, being less accustomed to exposure than the hands and arms, at least in temperate climates, greater precautions have to be taken to prevent vasoconstriction due to the exposure, especially of wet skin, to the air of the room. The legs are kept covered as far as possible down to the bath, and afterward down to the calorimeters. A somewhat higher bath temperature than that commonly employed for the hands is prob-

ably also advantageous for the foot measurements. The temperature of the arterial blood at the ankle is taken as 0.6° C. below the rectal temperature.

In general, measurements of the hand flow are to be preferred for obtaining information as to the condition of the circulation as a whole. It is in cases where the local conditions made it desirable to examine the foot flow, or where the patients were too ill to sit up for the hand examination, that foot flow measurements were undertaken. For the sake of comparison the hand flow was also measured wherever possible. It will be pointed out later that the ratio of the foot flow to the hand flow sometimes reveals interesting features.

SECTION II. RESULTS ON NORMAL PERSONS

A typical experiment on the feet and hands of M. C., a healthy man aged 24 years, height 5 feet 10 inches, weight 165 pounds, on whose hand flow numerous observations had been made, will illustrate the results obtained.

M. C., pulse (sitting) 98. Feet put into bath at 1.42 P.M. At 1.54 P.M. the subject lay down on his back. At 1.56 P.M. feet put into calorimeters. 2,775 c.c. of water in each calorimeter. The calorimeters as finally reduced in capacity were used.

Time.	Temperature (C.) of			Notes.	Time.	Temperature (C.) of			Notes.			
	Calorimeters.		Room.			Calorimeters.		Room.				
	Right.	Left.				Right.	Left.					
1.58	30.87	30.88	24.3		2.18	31.92	31.91	24.3				
2.00	30.97	30.93	24.3		2.20	31.99	31.96					
2.02	31.06	31.01			2.22	32.08	32.04	24.6				
2.04	31.18	31.14	24.3	From 2.04 to 2.06 stirring of left calorimeter insufficient.	2.24	32.10	32.10					
2.06	31.295	31.20		Pulse (lying down) 92.					Stirring of right calorimeter insufficient for the last minute.			
2.08	31.43	31.39	24.3									
2.10	31.57	31.51										
2.12	31.70	31.65	24.1									
2.14	31.795	31.75		At 2.14 subject sat up and continued sitting for rest of exper- iment.	2.26	32.18	32.18	24.6	At 2.30 right foot put in water at 8° C.			
2.16	31.87	31.82	24.2		2.32	32.37						
					2.32	32.32						

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Time.	Temperature (C.) of			Notes.	Time.	Temperature (C.) of		Notes.		
	Calorimeters.		Room.			Left	Left			
	Right.	Left.				calorimeter.	Room.			
2.34		degree 32.38	degree 24.6	Subject says the left foot feels colder than before.	2.56 2.58 3.00 3.02	degree 32.905 32.99 33.095 33.22	degree 24.6 24.7			
2.36	32.42	24.6			3.03			Temperature of right calorimeter 31.80 degrees At 3.06 foot removed from calorimeter.		
2.38	32.465	24.6			3.04	33.31	24.6			
2.40	32.495	24.6								
2.42	32.54	24.6								
2.44	32.60	24.6								
2.46	32.68	24.6								
2.48	32.73	24.6								
2.50	32.78			At 2.50 right foot put in water at 43°.	3.07 3.18	33.40 33.17		Pulse (sitting) 97.		
2.52	32.80	24.6						cooling of right calorimeter 0.52° in 31 $\frac{1}{4}$ minutes.		
2.54	32.86	24.6						Cooling of left 0.23° in 11 minutes. Volume of right foot 1,232 c.c., of left 1,195 c.c.		

Hands put into bath at 3.40 P.M. Hands put into calorimeters at 3.52. 3,015 c.c. of water in each calorimeter.

Time.	Temperature (C.) of			Notes.	Time.	Temperature (C.) of		Notes.		
	Calorimeters.		Room.			Right	Right			
	Right.	Left.				calorimeter.	Room.			
3.51 $\frac{1}{2}$	degree 31.10	degree 31.22	degree 31.32		4.11	degree 32.37	degree 24.4			
3.53	31.10	31.26			4.12	32.43				
3.54	31.18	31.32	24.3		4.13	32.49				
3.55	31.26	31.41			4.14	32.53	24.3			
3.56	31.35	31.50			4.15	32.595				
3.57	31.44	31.59			4.16	32.67		At 4.16 left hand put in water at 43° C.		
3.58	31.53	31.67	24.3		4.17	32.71	24.4			
3.59	31.63	31.76			4.18	32.74				
4.00	31.72	31.81	24.3		4.19	32.78				
4.01	31.795	31.895			4.20	32.83	24.25			
4.02	31.87	31.98			4.21	32.88				
4.03	31.91		24.3		4.22	32.93	24.35			
4.04	31.98				4.23	32.98				
4.05	32.02		24.4		4.24	33.03	24.3			
4.06	32.08				4.25	33.08				
4.07	32.14		24.5		4.26	33.125	24.3			
4.08	32.21				4.27	33.22		At 4.27 hand out of calorimeter. Temp. of left calorimeter 31.40°.		
4.09	32.27		24.3		4.53	32.90				
4.10	32.31									

Cooling of calorimeters, right 0.32° C. in 26 minutes; left 0.58° in 51 minutes. Volume of right hand 505 cubic centimeters, of left

485 cubic centimeters. Rectal temperature 37.1° C. Water equivalent of calorimeters with contents in feet observations, right 3,899, left 3,871. The corresponding numbers for the hand observations are, right 3,499, and left 3,483.

In this experiment the flow in the right foot was 5.11 grammes, and in the left 5.23 grammes per 100 cubic centimeters of foot per minute lying down, and only 3.96 grammes for the right, and 4.17 grammes for the left sitting up. In J. R., another normal young man, 20 years old, there was also a reduction in the flow in the sitting position, although less marked than in M. C. (from 7.98 and 7.58 grammes for the right and left foot, respectively, to 7.84 and 6.90 grammes per 100 cubic centimeters of foot per minute). This is of importance in connection with the fever observations, for it permits the assumption that the observed flows were at any rate as large as would have been obtained had the patients been sitting. These observations can therefore be safely compared with all the data obtained on normal persons. The flows in M. C. in this experiment agree with the results obtained nearly two years previously. This shows that when proper precautions are taken, the range of variation in the observed foot flow in one and the same healthy person is moderate, just as is the case for the hands. Therefore, when great differences, usually in the direction of deficiency, are found in pathological cases it can be assumed with some confidence that they are not due to accidental differences in the external conditions.

The reflex vasomotor effects from one foot to the other are similar to those obtained in the hands, only the constriction elicited by cold seems to be more durable. Thus in M. C. immersion of the right foot in water at 8° C. caused a diminution in the flow in the left foot from 4.17 to 3.12 grammes per 100 cubic centimeters per minute for the first ten minutes of the immersion. This gave place rather suddenly, as in the hand, to an increase in the flow (to 5.17 grammes per 100 cubic centimeters per minute) for the remaining eight minutes of the immersion. The greater susceptibility to vasoconstriction of the feet than of the hands has already been mentioned in connection

with the technic of the measurement since it introduces a possibility of error which must be carefully minimized or excluded, especially in pathological cases, for in not a few clinical conditions this susceptibility seems to be augmented. Where organic local changes are excluded a marked diminution in the foot flow due to vasoconstriction can usually be discriminated from a feeble flow in the feet due to deficient driving power in the circulation, by comparing the flow in the hands under the same conditions. For M. C. this was done in the experiment under discussion. The flow in the hands in the sitting posture amounted to 14.71 grammes per 100 cubic centimeters per minute for the right, and 15.10 grammes for the left. Even the greatest foot flow seen in this individual does not approach one-half of the hand flow per 100 cubic centimeters of tissue per minute. The average of four experiments on different dates for the right foot in the sitting position is 4.28 grammes. The average of nine already published² experiments on the hands of M. C. in the sitting position, suitable as regards the range of room temperature and comparable in other respects, is 12.77 grammes for the right hand, and 12.29 grammes for the left.

In Table I are given the condensed results of nine additional experiments on M. C.'s hands, the average flow in which is 12.95 grammes for the right hand, and 12.41 grammes for the left. If the observations of May 24, 1911, and November 27, 1911, be excluded, as obviously extreme results due to external temperatures which for the conditions of our experiments may be considered extreme, we get an average of 12.91 grammes for the right hand, and 12.61 grammes for the left.

In this man, then, the ratio of 1 to 3 holds approximately for the hand and foot flow as determined under our conditions. It is not pretended that the deficiency in the foot flow as compared with the hand flow is in reality exactly as great as this. As already pointed out, the difference between the observed and the actual flow in the foot may be expected to be greater than the corresponding difference for the hand on account of the difference in the dimensions of the two parts. The smaller the

² Stewart, G. N.: *Heart*, 1911, iii, 33.

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TABLE I.

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TABLE I.—Continued.

Date.	Age in years.	Pulse rate.	Blood pressure.	Room.	Arterial blood.	Calorimeters.	Temperature (C.) of	Normal Individuals.						Notes.						
								Left.	Right.	Left.	Right.	Left.	Right.							
May 22, 1911	22	80					28.9	31.15	31.21	41.6	41.0	3.975	4.176	16	50.65	53.83	12.20	13.13		
							28.0	31.76	31.96	4.97	4.028	6	28.52	6	6.95					
							28.0	31.96			6	41.03		9.89						
C. B. Hands.	Nov. 17, 1911	106	103				29.1	32.36	30.16	30.29	43.0	42.6	2.022	2.712	8 ¹	48.17	49.22	57.09	11.45 ¹	13.46 ¹
	Nov. 20, 1911	113					24.8	36.5	30.68	30.66	41.0	40.5	2.388	1.334	10	26.36	25.55	6.43	6.30 ¹	
	Nov. 21, 1911	104					24.2	36.75	31.28	31.36	41.0	40.5	2.096	2.060	9	47.30	46.83	11.54 ¹	11.42 ¹	
	Nov. 24, 1911	80	116				23.5	36.6	30.48	30.40	40.0	38.5	7.85	9.93	6	23.56	28.46	5.89 ¹	7.39 ¹	Hands felt cold though not to the subject.
C. B. Foot.	May 2, 1911	72					26.3	36.3	30.02		9.80		1.673		6	46.38	47.3			
							26.3	30.20					1.445	1.216	4	52.14	5.32			
							26.0	30.36							4	56.82	5.79			
	(Mar. 22, 1913)	20	52				24.0	36.0	30.90	30.88	39.7	35.4	2.388	1.537	13	40.02	25.60	10.08	7.25	
							24.2	31.30					1.092	1.192	13	19.85				
							23.95	31.42					1.113	1.113	2	13.70	3.45			
							23.9	31.49					40.9		3	33.59	8.46			
							23.95	31.72					1.610		7	59.70	15.04			
J. R. Hands.	Mar. 25, 1913	62	101, 60				24.8	36.5	31.62	31.55	39.3	37.6	3.206	2.217	15	48.86	33.17	12.38	8.82	
							24.4	32.11					400	802	5	23.28	5.92			
							24.4	32.25					1.092	1.092	41.93	10.67				
							24.4	32.37					347		3	31.11	7.91			
							24.5	32.61					1.699		7	69.32	17.64			
J. R. Feet.	Mar. 25, 1913	76					25.1	36.4	31.54	31.40	1.008	9.68	4.925	4.580	14	80.42	72.70	7.98	7.58	Lying on back.
							24.6	32.60	32.34				4.869	4.869	18	79.09	66.27	7.84	6.90	Sitting.
							24.45								1.440	45.32	4.72	4.72	R. foot in cold water.	
							24.45								1.405	58.77	6.12	6.12	Foot in warm water.	
							24.45								1.753	79.82	8.27	8.27	Foot still in warm water.	

¹ The cuffs of the sphygmomanometer were on the arms, but were not inflated. In preparing the lecture for publication some observations made since it was delivered have been included.

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TABLE I.—Continued.

N. R.	Apr.	8, 1913	84	84	Blood pressure.	Pulse rate.	Age in years.	Normal Individuals.		Fever Patients.		Notes.	
								Room.	A arterial blood.	Right.	Left.	Height.	
								Temperature (C.) of	Calori-meters.	Volume of part in c.c.	Heat given off in small calories.	Blood flow per 100 c.c. of part per min. in gm.	
								degree	degree	degree	degree	degree	
								24.0	36.7	30.97	31.10	203	181
								24.0	36.8	30.98	30.88	491	480
												1.292	1.226
												15	16
												16.70	16.21
												15	13.72
												15	3.37
												2.86	8.95
												Hands.	Feet.

¹ The flow was so small that even after the feet had been in the calorimeters for 21 minutes the loss of heat by the calorimeters to the room was not yet balanced. The feet were withdrawn before usable readings were obtained. From the readings obtained it is practically certain that the foot flow was not greater than on October 16.

foot the closer must the observed come to the actual flow. Yet the error due to this is apparently not great, as is indicated by the comparison of the hand and foot flows in a boy, N. R., 8 years and 9 months old. The observations on him were made for the purpose of testing this point. The volume of his feet is no greater than that of M. C.'s hands, in fact somewhat less, and the average thickness of the skin even including that of the soles is probably less. Although the greatest thickness of the boy's foot is probably somewhat greater than the maximum thickness of M. C.'s hand, the dimensions of the two objects do not differ sufficiently to forbid the assumption that the equalization of temperature of the boy's foot and the man's hand with that of the calorimeter would be about equally complete. If then the flow in the adult foot as estimated in this method were much below the actual flow, the measured flow in the boy's foot should approach much nearer to that in his hand than is the case in the adult. Yet the ratio was practically the same as in M. C.

From all the observations on the foot flow the following conclusions seem permissible.

1. The blood flow in the foot is smaller per unit of volume of the part than in the hand, the ratio of foot flow to hand flow per 100 cubic centimeters of the part usually ranging in normal persons from 1 to 3 and 1 to 2.

2. In the supine position, with the legs hanging down, the flow in the feet seems to be somewhat greater than in the sitting position.

The changes produced in the flow in normal persons by changes in the physiological condition of the part, or in the external temperature, or by mechanical interference with the circulation, can be readily followed by this method. The higher the room temperature, the greater in general is the flow. When this factor is taken into account the results on different days, with similar calorimeter temperatures, in one and the same individual, leading a uniform life, do not differ greatly, although different individuals when tested under apparently similar conditions show a much greater range in the blood flow. Some normal persons know and say that their hands are habitually cool or cold, others that their hands are habitually warm. The

former will have a relatively small and the latter a relatively large flow of blood in the hands as estimated by this method.

The influence of muscular contraction in increasing the flow is easily demonstrated. Thus with a calorimeter temperature of about 24.38° C. and 23.64° C. for the right and left hand respectively and a room temperature of 21° C., the flow was 15.4 grammes per 100 c.c. per minute for the right hand while it was being made to contract in the calorimeter and only 4.9 grammes for the left, which remained at rest. Since 4.9 grammes is a much smaller flow than was ever found in this person, M. C., with both hands at rest, the increased flow in the contracting right hand is accompanied by a diminished flow in the contralateral hand.

The diminution in the flow caused by a moderate degree of obstruction to the venous circulation (a rubber band constricting the wrist, but not very tightly) can also be very simply measured. Thus, in an experiment on one of the normal persons, the flow in the left hand, which had been 13.2 grammes and 13.1 grammes per 100 c.c. per minute in two experiments immediately preceding the constriction, was diminished to 4.2 grammes per 100 c.c. per minute for the first four minutes after constriction. For the next six minutes the flow rose to 9.3 grammes per 100 c.c. per minute, owing, of course, to the gradual increase of the venous pressure distal to the band, which enabled the obstruction to be more and more successfully overcome. The high initial flow observed in this person was due to two factors, (a) a relatively high room temperature (24° C.), (b) the fact that the cutaneous circulation of this individual is habitually copious.

In another experiment (on M. C.) in which the upper arm was compressed on the right side by inflation of the cuff of an Erlanger sphygmomanometer, the flow for the right hand fell from 8.74 grammes to 4.52 grammes per 100 c.c. per minute. The initial flow was unquestionably diminished somewhat, even by the application of the cuff, without inflation, for at the same time the flow in the left hand was 10.83 grammes per 100 c.c. per minute.

In this connection may be mentioned experiments in which

the flow was tested in a normal man, M. C., after bandaging one hand so as to cause temporary anaemia of the part, or after bandaging of one forearm so as to cause temporary congestion of the hand. In both cases the bandage was removed just before the hands were put into the calorimeters.

In an experiment in which the left hand had been rendered anaemic the calculated flow was 7.45 grammes per 100 c.c. of hand per minute for the left hand, against 6.26 grammes for the right. In an experiment in which the left hand had been rendered passively congested the calculated flow was 11.61 grammes per 100 c.c. per minute for the left hand and 12.86 grammes for the right for the first nine minutes in the calorimeters. For the second nine minutes the flows were respectively 10.96 grammes and 13.78 grammes for the left and right hands.

Certain questions connected with the clinical measurement of blood pressure may also be investigated by this method. For instance, it was concluded, on the basis of observations on two healthy young men, that a pressure equal to the systolic pressure, as estimated by the clinical methods used, applied to the upper arm by a broad cuff, causes complete cessation of the blood flow in the hand. Since the pressure in the veins distal to the constricting armlet eventually becomes equal to the systolic arterial pressure, this was taken to mean that the lumen of the arteries under the cuff is actually obliterated, a question concerning which there was some doubt. From the same investigation the following points were also determined.

1. When the pressure in an armlet compressing the upper arm is reduced from the systolic arterial pressure the blood flow in the corresponding hand is only slightly increased for a considerable decrement of pressure.

2. The pressure in the armlet must fall somewhat below the "diastolic" pressure, as clinically determined, before any marked increase in the flow through the hand occurs.

3. The first decrements of pressure below this "critical" pressure are accompanied by a much greater increase in the flow through the hand than further equal decrements.

4. A handicap of half the "diastolic" pressure causes only a relatively small diminution in the flow through the hand; and

it was suggested that the method of handicapping the circulation in the arm or leg by known pressures and observing in what degree the handicap is overcome, may in certain cases constitute a useful supplementary method of clinical investigation.

The influence of direct heating of the hand (high bath and calorimeter temperatures) in increasing the flow is also followed without difficulty. Thus, in three experiments on the same person with calorimeter temperatures above that of the arterial blood the flows were, without exception, the greatest measured in the whole series of observations, viz.: 16.3 grammes per 100 c.c. per minute with calorimeter temperature 39.6° C., 16.5 grammes with calorimeter temperature 41.5° , and 18.3 grammes with calorimeter temperature 39.09° C., all for the left hand. Where the calorimeter temperature is above that of the arterial blood the blood abstracts heat from the calorimeter, instead of giving off heat to it, and it is from the *fall* of temperature in the water (corrected of course for the loss of heat to the surroundings) that the flow has to be calculated.

The effect of forced breathing on the blood flow in the hand was tested in two normal persons. It was found to distinctly diminish it. The increase in the respiratory movements was by no means excessive. Yet in one case, M. C., the flow fell from 12.66 grammes to 8.62 grammes per 100 c.c. of hand per minute for the right hand and from 12.76 grammes to 9.20 grammes for the left hand, to rise again when breathing became normal. In the other case, C. B., the relative change was even greater although the initial flow was less. It would lead us too far to discuss here the significance of this result. One might think of the acapnia caused by the washing out of the carbon dioxid as a possible influence. Mechanical changes in the thorax, and particularly those affecting the filling and discharge of the heart, must also be taken into account. One moral to be drawn is that while the respiratory pump plays a part of some consequence in the normal movement of the blood, and may even become the preponderant factor when the heart and the vasomotor mechanisms are crippled, the idea of the "deep-breathing" fanatics that voluntary interference with the exquisitely regulated

respiratory mechanics *must* be good receives no support, at least so far as the circulation in the periphery is concerned.

Coming now to the observations on clinical cases, a few general remarks may be of use.

General Remarks.—The material studied consisted of patients in the Dispensary of Western Reserve University and Lakeside Hospital, and the private practice of friends. The major portion of the material was from the wards of the City and other hospitals. Comparable results are much more easily obtained in successive observations on hospital patients whose surroundings and regimen are fairly constant, and fewer precautions necessary than on dispensary or private patients. In particular the influence of the external temperature, the factor which of all others among the external conditions is most apt to influence results, is much more easily controlled in the case of the hospital patients, especially in winter. The observations on the latter were made in a room in the hospital to which the patients were brought in the wheel chair, or the movable bed, or to which if well enough they walked. As is true for many kinds of physiological clinical examination the observations are more satisfactorily made in a separate room than in the open wards. Where the external conditions are controlled and the clinical state of the patient has not altered noticeably, the results of the blood flow measurements from day to day, and, indeed, from week to week, show a very fair and often a surprising degree of constancy. Not only is the hospital patient in a temperature which varies comparatively little, but his diet is also controlled and the general regimen under which he lives is relatively stable. In any of the hospital cases the approximate constancy of the flow was not only seen in one and the same hand, but also in the proportion between the flows in the two hands where a conspicuous difference existed. As regards the dispensary material, care had to be taken in winter that the person was long enough in the room before the observations were begun, especially if he came to the dispensary with bare hands. It is true that if the flow were immediately measured a result would be obtained which would give the flow correctly enough for the given condition of the hands but it would be useless as an expression of the flow under the approximately standard conditions which have to be established if comparison of the flow in the same patient at different times or in different patients is proposed. In summer the factor of external temperature presents no difficulty in dealing with dispensary patients.

**SECTION III. OBSERVATIONS IN CASES WITH OBVIOUS DIFFERENCES
BETWEEN THE TWO HANDS OR FEET**

In addition to the clinical interest which attaches to the measurements in the individual cases dealt with in this section, the material was chosen partly as a test of the technic of the method, as in many of the cases the qualitative difference between the two sides could be foreseen from the anatomical difference which existed.

In a man 21 years old, with healing burns on both hands but more extensive on the right, the flow was 7.04 grammes per 100 c.c. per minute for the right hand and 5.44 grammes for the left hand (for the last nine minutes in the calorimeters) with an average room temperature of 25° C. The burned areas on both hands were quite red, and taking the whole surface of the hands into account the vascularity of the superficial layers must have been considerably greater in the right than in the left hand. In both hands many blood-vessels in the new tissue must be nearer the surface than in the normal hand, a point of interest in connection with the technic of the method (Heart, 1911, iii, 55). In spite of the red color both hands felt rather cold to the touch, and this agrees perfectly with the tardiness with which the thermometers rose at first and with the calculated blood flow, which for the man's age and the room temperature is subnormal. The redness is due to the number of capillaries in the healing areas and to the fact that they lie just under the surface, not to a great flow of blood through widely dilated vessels. The case presented an opportunity for studying the flow in blood-vessels which have not long existed and whose vasomotor connections may be still incomplete or immature. Immersion of the left hand in warm water caused a marked increase, and subsequent immersion of the left hand in cold water a marked decrease in the flow in the right hand. The persistence of both reflexes was remarkable. Another peculiarity observed in only one other case, in which one of the hand nerves had been divided and had not apparently completely regenerated, was that the temperature of the right hand calorimeter

during the immersion of the left hand in the warm or cold water showed abrupt changes; for instance, a sudden rise of the thermometer between the third and fourth minutes of immersion of the left hand in the cold water. The patient denied that his hand ever touched the thermometer, and from the position of the thermometer in the calorimeter contact of the hand with it can scarcely occur unless the hand is executing extensive groping movements of which there was no sign in these observations. The most plausible explanation of the phenomenon would seem to be that in the new blood-vessels, although the vasomotor connections had been established, there is still an abnormal vasomotor instability. The intensity of the total reaction may be due either to hyperexcitability of the receptive surfaces of the left hand (afferent path) or to hyperexcitability of the newly formed vasomotor endings, including the muscle of the new blood-vessels (efferent path), or to both.

In a man 42 years old, suffering from a malignant tumor of the right forearm (with metastases), with some oedema of the forearm down to the wrist, the flow in the right hand was 4.69 grammes per 100 c.c. of hand per minute, in the left hand 5.13 grammes, with an average room temperature of 23.2° C. The right hand was not swollen, as shown by the measurement of its volume. The deficiency in the right hand was an actual deficiency and not merely an apparent one, owing to the reckoning in of oedema liquid in the volume of the hand, since by measurement the right hand was only 3 c.c. larger than the left. It is therefore probable that the deficiency was due to the interference of the tumor with the venous return from the hand. In so far as it was not connected with inflammatory changes, the oedema was also probably caused by interference with the venous flow. In certain cases the blood flow measurement might help to settle the question whether oedema is due to obstruction on the lymph path or on the venous path. Obstruction confined to the lymphatics might cause oedema without diminution in the blood flow. Where a tumor is confined to the bone, obstruction to the flow of blood in the hand may be expected to be less marked than where it has extensively invaded the soft tissues.

A condition where oedema coincided with obstruction to the lymph flow not involving the venous flow seems to have been realized in the case of Charles B., a man 47 years old, in whom the diagnosis of Hodgkin's disease was made. He entered the hospital with both legs and feet greatly swollen. The swelling was stationary and little, if at all, diminished in the morning. During his entire stay in the hospital the swelling of the legs remained unchanged. There was no oedema elsewhere and no evidence of any lesion of the heart or kidneys. He had always lived in Cleveland. All the palpable lymph glands were enlarged. The blood flow in the right foot was 2.34 grammes per 100 c.c. of foot per minute, or allowing for the oedema fluid 3.04 grammes, and in the left foot, 2.50 grammes (allowing for the oedema fluid 3.24 grammes), with average room temperature of 22.7° C. These flows are by no means small for the feet. Indeed, in comparison with the hand flows (2.82 grammes for the right and 3.22 grammes for the left hand) they are quite large. A certain degree of anaemia, some cyanosis and dyspnoea were present, and this may contribute to the small hand flow (Stewart, *Journal of Experimental Medicine*, 1913, xviii, No. 2). It may be supposed that this would tell equally on the blood flow through the feet, but, in the absence of special observations on this point, we cannot be certain whether the compensatory vasoconstriction in anaemia is not greater in the anterior limb than in the posterior limb. It is conceivable that the circulation in the anterior limb has a closer association with the pulmonary circuit than the circulation in the posterior limb. That the hands were exceptionally liable to vasoconstriction was shown by separate observations, which gave a still smaller flow. It is rare to find a case in which the flow per 100 c.c. of foot per minute comes out as great as the flow per 100 c.c. of hand per minute in the same individual. In the vast majority of clinical cases the hand flow greatly preponderates, and this is the invariable rule for normal persons so far as our experience goes (*Journal of Experimental Medicine*, 1913, xviii, p. 354).

Interference with the local circulation would seem to be excluded in this case as a cause of the oedema of the legs. It is

more likely, indeed, if we take account of the hand flows that there is a local acceleration of the blood flow in the legs, perhaps through partial paralysis of their vasoconstrictors by the pressure of the same masses if mechanical pressure is responsible for the edema. If we confine ourselves to the question, leaving out all other possibilities, whether the edema is dependent on venous or on lymphatic obstruction the blood flow measurements give an answer unequivocally in favor of lymphatic obstruction, to this extent supporting the diagnosis of Hodgkin's disease.

Charles W., a man aged 42 years, a clerk, admitted to City Hospital October 29, 1912, had rheumatism at the age of 8 years, since which time the left leg seemed to be weaker and smaller than the right. At that time the arms and legs were somewhat swollen and extremely sensitive. He had a "stroke of paralysis" in 1903. Both arms and legs were affected. In seven months he had recovered from the stroke and had no trouble in walking or otherwise until 1907, when he had a second stroke. It took four years for his complete recovery from the second attack. Four months before admission he fell on the sidewalk and abraded the left shin about three inches. It healed somewhat. It kept partially healing and opening again and the pain continued so that he could not sleep. There are many petechial spots on left leg. Reflexes increased in the left leg. The left leg is atrophied and much smaller than the right and one and a half inches shorter. The left foot is not small, although doubtless smaller than the right. It is the lower leg which is conspicuously small.

I was asked to make an examination of the flow in the feet. The flow in the right foot was 1.89 grammes per 100 c.c. per minute and in the left 1.72 grammes with average room temperature 23.9° C. From this practical equality it was concluded that there was no obstruction in the main arterial supply of the left leg which could account for the slow healing of the sore and for the pain in the leg. If the cause was vascular it was therefore a vasomotor affair. Undue susceptibility to vasoconstriction might account for the relatively small flow in both feet. The slow increase in the flow in the left foot at the beginning of the observations supports the view that it was peculiarly susceptible to vasoconstriction. The cause of the small flow was not a central one (deficiency in the driving power of the heart), since the flow in the hands was normal (10.62 grammes for the right per 100 c.c. per minute and 10.00 grammes for the left with room temperature 23.9° C.).

On discharge he was able to use the left foot better than for seven years.

Some interesting cases in which obvious differences between the two hands exist were found in tubercular inflammations. Of these we shall cite three. One in which the inflammation was due to an infected finger, one in which it was due to gout and a third in which it was due to a sprain.

A man aged 46 had an infection of the right hand with considerable swelling and redness. Otherwise he was in good health. The protein has been already published (Early, 1911, *ibid.* p. 21). The flow was 11.30 grammes per 100 ml. per minute, or allowing for the plasma found to be 3 grammes in the right hand against 2.91 grammes in the left, with room temperature 28.5°. There can be no doubt that there will be increase in the flow in the infected hand in this case, there goes a decrease in the flow in the normal hand since 2.91 grammes is an unusually small flow for a healthy man of this age. The suggestion is that in order to provide for the increased flow in the infected hand a vasodilation is possible, caused mainly through the pain nerves of the infected hand, or perhaps more elsewhere and particularly in the sympathetic pained parts on the opposite side.

However this may be, a fact of great interest is noted when the tissues are taken from the left or the right hand are studied. Immersion of the left hand in cold water caused scarcely any reduction of the flow in the right hand from 11.30 to 11.11 grammes, or allowing for the plasma found from 11.6 grammes to 11.3 grammes. This is a very small change indeed and suggests that the protective impulses to the infected part are so great as possibly to dilate impulses to the normal part. It is a well known fact that the vasomotor nerve endings of the sympathetic nerves are of such great importance in the reaction between them and the hormones. It is clear that such a blood flow is a most valuable protection against infection and that the protective impulses so to set the full stream of blood which is so important a factor in combating the infection.

Immersion of the left hand in warm water also caused hardly any increase in the flow through the right hand beyond

promptly removing the small effect of the cold water. But this is of less interest, as the vasodilatation in the infected hand was probably already nearly maximum, and it is usual to obtain a relatively small reflex vasodilatation in a hand with a large initial flow. It is, however, again of interest that the initial vasoconstriction which normally follows immersion of the contralateral hand in warm water is here absent, a further indication of a block on the vasoconstrictor path. A very different picture is presented by the case of gouty (non-bacterial) inflammation in which two examinations were obtained.

The patient was a man aged 50 years. He had suffered from gout for twenty years. There were tophi in the scrotum as well as in the ears. The right wrist and hand were swollen and painful.

At the first examination, on April 3, 1912, with room temperature 24.3° C. the flow was 6.88 grammes per 100 c.c. of hand per minute, or allowing for the swelling 7.47 grammes in the right hand and 3.07 grammes in the left. Immersion of the left hand in warm water caused the usual diminution of the flow in the right; to 4.66 grammes (allowing for swelling 5.06 grammes), followed by an increase to 9.88 grammes (or allowing for the oedema 10.73 grammes), a good vasodilatation. It must, of course, be remembered that the initial flow in the right hand did not correspond with anything like a maximal vasodilatation. It is therefore all the more significant that immersion of the left hand in cold water caused a marked and persistent decline of the flow in the right hand to 3.84 grammes (or allowing for the swelling to 4.16 grammes). There is then in this case of non-bacterial inflammation no sign of vasoconstrictor block.

The same fact comes out fully as well in the second examination (July 9, 1912), which was made on a very warm day with a room temperature of 29.7° C. The right hand was much more swollen at the second examination than at the first. At neither examination was there any pain in the left hand. The initial flow was 13.27 grammes (taking only the flow corrected for the oedema liquid) in the right and 8.13 grammes in the

left hand. As compared with the previous examination, the flow in the left hand is of course proportionately more increased by the high external temperature than that in the right. It is still, however, for the temperature a distinctly subnormal flow. On immersion of the left hand in cold water, the flow in the right was diminished to 8.47 grammes, a very fair reaction in the normal direction, and this flow mounted to 12.82 grammes, nearly the initial flow, on subsequent immersion of the left hand in warm water.

It would not be profitable to speculate upon the reasons for the difference in the reflex vasomotor reactions in the two cases related further than to point out that the local infection is an acute affair, a bacterial invasion fraught with imminent peril to the organism if it be not promptly dealt with. The mechanism exists, and in the blood, for the effective and rapid destruction of the bacteria. On the other hand, if the essential condition of the gouty paroxysm be the deposition of urates in the tissue, while an increase in the blood stream may doubtless be of value in aiding the tissue to segregate the deposit so as to minimize its action as a mechanical irritant, no increase in the blood flow however great and however sustained will soon effect the re-solution of the deposit, which in any case is quite indifferent to the body as a whole and exposes it to no danger of invasion.

The third case was that of a man aged 66 years, who had sprained the little finger of his left hand three days before the examination. The hand was swollen but not greatly. He said the pain had diminished. The difference in flow between the two hands was very striking (1.7 grammes per 100 c.c. per minute for the right hand and 5.2 grammes for the left with a room temperature of 23.4° C.). The flow is small in both hands, which is accounted for by the arteriosclerosis (see Paper XI of this Series, Archives of Internal Medicine, 1913), the renal disease, and the age of the patient. It may be worth pointing out once more that a high systolic arterial pressure such as existed in this patient, far from indicating a copious flow, is commonly the index of a high peripheral resistance coupled with a small flow.

No observations were made on the vasomotor reflexes, although it would have been interesting to compare this case of traumatic non-bacterial inflammation with one of infection. The complicating conditions, however, especially the arteriosclerosis which tends to prevent marked vasomotor reflexes, rendered the case an unfavorable one for these tests.

Among the most interesting cases in this section are certain instances in which congenital or at least very long standing anatomical defects existed in one hand without markedly affecting its functional power. Here, as was to be expected, no great difference in the flow per 100 c.c. of hand was made out.

A girl 21 years old, who works with a sewing machine in a factory, came to the Dispensary for "nervousness." She has suffered much from headache the past two or three months. Her left wrist is deformed, the styloid process of the ulna being very prominent, and the left hand is considerably smaller than the right. This difference is possibly due to rheumatism, but she has had it a long time, perhaps even from birth. The left hand is normally formed and she uses it in all ways in which a normal hand would be used, only it is not so strong as the right hand. The left anterior limb is shorter than the right and the girth of the forearm is distinctly less to the eye. The left hand does not get cold any more than the right and does not require to be better protected in winter. The pulse at the wrist is of fair volume to the finger.

With the rather high room temperature of 26° C. the flow in the right hand was 9.08 grammes per 100 c.c. of hand per minute, in the left 8.81 grammes.

A man aged 46 years, with spastic paralysis of the left wrist (birth palsy), showed a flow in the left hand but little less than that in the right (right hand 10.71 grammes per 100 c.c. per minute, left hand 10.2 grammes with room temperature 20.5° C.). These flows are perfectly normal. He uses the left hand largely in his work, that of a telegraph operator. It was obviously well supplied with blood.

A girl, 15 years old, congenitally deficient in intellect, was brought on this account to the Dispensary by her mother. Her

left hand is congenitally defective, the thumb being wanting; otherwise it is perfectly formed, though small. The left arm, both upper and lower, is much smaller in girth than the right, and the elbow-joint appears very prominent between the two ill-developed segments. The left hand easily gets cold in winter. She uses it quite freely but not so much as the right. The whole left anterior extremity is somewhat shorter than the right.

With room temperature 26.5° C. the flow in the right hand was 5.96 grammes per 100 c.c. per minute, and in the left 6.6 grammes per 100 c.c. per minute. The flow in the defective hand is thus somewhat greater than in the normal one in contrast to the condition in a case of infantile paralysis in a boy 9 years and 6 months old, whose left hand was much atrophied and functionally of little use. In his right hand the flow was 15.0 grammes per 100 c.c. of hand per minute against 7.6 grammes in the left hand with room temperature 23.4° C.

A man aged 51 years had suffered amputation of the whole middle finger and the second and third phalanges of the index finger of the left hand for an injury. The proportion of skin in the left hand was thus considerably reduced. I have shown that the flow in the distal half of the hand is much greater per unit of volume than in the whole hand. It was to be expected, therefore, that the flow in the left hand in this case should be decidedly less than in the right. The expectation was realized, the flow in the right hand being 7.20 grammes and in the left 5.34 grammes with room temperature 24.5° C. The flow in the right hand is probably subnormal, as the patient had pulmonary tuberculosis with right pleural effusion, which had been aspirated two days before the examination (see p. 148).

The last case to be mentioned in this section is that of a woman 68 years old in whom Dr. Carl Hamann had ligated the innominate and right common carotid arteries for aneurism of the subclavian artery with a successful result. A month after the operation the blood flow in the two hands was compared on two successive days. No pulse could be felt in the right wrist or over the course of the right brachial. She says the right hand gets cold if left uncovered with the bed-clothes.

On being emptied, by stripping, the veins on the back of the right hand fill slowly from below. The right hand can execute all movements, but it is weak. There is some paraesthesia (pins and needles and numbness) in the right hand, but this she had before the operation, and it has not been intensified since. The nails on the right hand are getting clubbed. She has noticed that they are getting "like those of a man." The change in the nails was present before the operation, but is now more marked.

The calculated blood flow at the first examination was 5.32 grammes per 100 c.c. per minute for the left hand and 1.50 grammes for the right (ratio of right to left 1:3.54). The next day the flows were 5.85 grammes and 1.68 grammes per 100 c.c. per minute for the left and right hands respectively (ratio 1:3.48). Immersion of the left hand in warm water produced practically no effect on the flow in the right. It is obvious from the anatomical conditions that dilatation of the vessels of the right hand, even if it occurred, could scarcely aid the scanty collateral flow.⁸

SECTION IV. THE ANÆMIAS

Anæmia has a special influence, which it is essential to make clear, on the flow in the peripheral parts. Therefore, a number of clinical cases illustrating the anæmias will next be taken up.

The common characteristic of the anæmias as regards this point is a small flow in the hands as compared with a normal person of similar age and under similar external conditions. Thus in H. W., a case of pernicious anæmia with an erythrocyte count of 2,000,000 in a man 24 years old and with room temperature 23.5° C., the flow was only 2.06 grammes per 100 c.c. of hand per minute for the right hand, and 1.82 grammes for the left—i.e., only one-third to one-sixth the amount to be expected in a healthy man of the same age under like conditions.

⁸ Four months later the flow in the right hand had improved so much that the ratio of right to left was 1:1.3 and the vasoconstrictor reaction from left to right hand was distinct. It was concluded that certain symptoms were not due to anæmia of the right hand and arm but to pressure of callus on the brachial plexus and that a further operation for their relief was therefore not contra-indicated.

In another case of pernicious anaemia, D. K., in a man 44 years old, the flow on an extremely hot day with room temperature 29.1° C. rose to 8.35 grammes per 100 c.c. per minute for the right hand, and 8.38 grammes for the left, whereas in the healthy young man, M. C., already referred to, the flows were respectively 17.98 grammes and 16.65 grammes with room temperature 27.1° C. In health, so far as our observations go, the flow is not inferior at the age of forty-four years to that at the age of twenty-two. The room temperature was one of the highest worked with in the whole series of observations and the calorimeter temperature was also relatively high. There is of course a cutaneous vasodilatation in response to the high external temperature, else life would be endangered, yet the hand flow in D. K. remains markedly subnormal. It is perfectly intelligible that under these conditions the further reflex vasodilatation under the influence of warm water applied to the contralateral hand is feeble, the flow increasing only to 9.10 grammes per 100 cubic centimeters per minute, while the reflex to cold is intense, the flow diminishing to 2.85 grammes. Blood examination gave erythrocytes 1,648,000, haemoglobin 45 per cent., color index 1.4. The erythrocytes showed marked variation in size, polychromatophilia; punctate basophilic cells; nucleated reds.

In a case of marked secondary anaemia, S. K. (erythrocytes 2,112,000, haemoglobin 45 per cent.), associated with carcinoma of the uterus in a woman forty-eight years old, the flow was only 1.26 grammes per 100 cubic centimeters of hand for the right, and 1.18 grammes for the left hand (for the last ten minutes in the calorimeters) with a room temperature of 23.3° C. She died 11 weeks later.

In a young man of 22 years, F. W., the subject of haemophilia, the flow was 5.04 grammes per 100 cubic centimeters per minute for the right hand and 3.94 grammes for the left (for the last fifteen minutes in the calorimeters) with room temperature at 24.7° C. The flow was scarcely at all increased reflexly by the application of warm water to the contralateral hand, although it was easily decreased in the case of the right hand to 2.79 grammes per 100 cubic centimeters per

minute by the application of cold water to the left hand. At the time of the blood flow examination there had been no hemorrhage for six weeks.

In Mrs. M. A., a woman 38 years old, with an erythrocyte count of 3,000,000 and a haemoglobin percentage of 80, in whom a diagnosis of cirrhosis of the liver was made, the flow was 4.70 grammes per 100 cubic centimeters per minute in the right hand, and 5.44 grammes in the left hand (for the last thirteen minutes in the calorimeters) with room temperature 23.1° C., a flow below the normal for her age. The tardiness with which the point was reached at which the thermometers began to rise uniformly, indicating stubborn vasoconstriction, well illustrates a common characteristic of this group of cases. The consequence of this tardiness is that if we reckon the blood flow for a period of twenty-two minutes it comes out only 4.02 grammes per 100 cubic centimeters per minute for the right hand and 4.64 grammes for the left.

In three cases of the chlorotic type the flow although probably below the normal was by no means scanty. Thus in E. D., a girl of 16 years with an erythrocyte count of 4,100,000 and a haemoglobin percentage of 50, the flow in the right hand was 6.25 grammes per 100 cubic centimeters per minute, and in the left 5.76 grammes (for the last thirteen minutes in the calorimeters) with room temperature 22.2° C. The contralateral vasodilatation produced by warmth was slight, the contralateral vasoconstriction produced by cold much more distinct.

In A. P., who are still nursing completely her 13-months-old baby, the red cell count was 4,600,000; the haemoglobin 70 per cent., the flow in the right hand 8.75 grammes per 100 cubic centimeters per minute, and in the left 8.09 grammes with room temperature 23.5° C.

In Mrs. T., a woman aged 30 years, with an erythrocyte count of 4,584,000 and a haemoglobin percentage of only 40, the flow in the right hand was 6.48 grammes per 100 cubic centimeters per minute and in the left 7.20 grammes with room temperature 22.6° C.

In a case of anæmia secondary to copious gastric hemor-

rhage in O. L., a man aged 36 years, the erythrocyte count was 2,250,000, the haemoglobin percentage 45, the flow in the right hand 7.02 grammes per 100 cubic centimeters per minute, and in the left 6.90 grammes, with a room temperature of 25.4° C. For the age of this man and the relatively high room temperature, these figures are rather small, but very much higher than in H. W. and S. K., where the anaemia is associated with much graver general changes than in O. L., whose blood changes were probably at this time conditioned mainly or entirely by the hemorrhage. The contralateral vasodilatation to warmth was good, the flow in the right hand being increased from 7.02 grammes to 9.93 grammes per 100 cubic centimeters per minute when the left hand was immersed in warm water after the usual preliminary diminution (to 5.95 grammes). The reaction to cold was fair.

More than two years from the time of the first large hemorrhage he was still alive, but an inoperable carcinoma of the cardia had been found.

In a case convalescing from scurvy, J. B., a man 34 years old, the flow in the right hand was 5.53 grammes per 100 cubic centimeters per minute, and in the left 6.30 grammes, with room temperature 23.9° C. The vasomotor reflexes were good, the flow in the right hand increasing to 10.47 grammes (after a preliminary dip to 2.54 grammes for the first minute), when the left was immersed in warm water, and sinking to 5.66 grammes for the first three minutes of immersion of the left hand in cold water. For the two minutes succeeding the first minute of immersion of the left hand in cold water the flow in the right was only 4.68 grammes per 100 cubic centimeters of hand per minute.

On admission to the hospital three weeks before the blood flow examination was made the haemoglobin was 60 per cent.

Finally, in a case of severe nose-bleed, in G. L., a man 26 years old, otherwise in good health and without symptoms, the flow was normal (10.27 grammes per 100 cubic centimeters per minute for the right hand, and 10.40 grammes for the left) with room temperature 24.2° C. The erythrocyte count was 4,256,000.

Plesch has stated that the output of the left ventricle per minute (the minute volume), measured by a gasometric method, is increased in the cases of anæmia investigated by him, including pernicious anæmia, chlorosis, and secondary anæmias. His explanation is that the deficiency of hæmoglobin entails the circulation of a greater quantity of blood through the lungs in order that the oxygen requirement of the body may be filled. He does not discuss the mechanism by which this necessary increase in the minute volume is obtained. My observations on the hand flow indicate in an interesting manner that an important, if not the sole, way in which the increased minute volume of the heart is rendered possible is the diminution in the flow through the periphery by vasoconstriction. This obviously will shorten the average circulation time of the blood and permit its quicker return to the right heart and therefore its more rapid circulation through the lungs. It is to be expected that the cutaneous vessels should be particularly affected by this vasoconstriction. For in the main the blood circulates in the skin, not in the interests of the nutrition of the skin itself, for which a comparatively small flow would suffice, but to regulate the loss of heat. Where it is important that the blood should pass in a fuller stream than ordinary through the lungs it can accordingly be readily spared from the peripheral layers of the body. Since the metabolism in the anæmic body is usually less than normal, a smaller cutaneous circulation than normal is in any case required to eliminate the heat produced. If the peripheral vasoconstriction is accompanied by a vasodilatation in the deeper and shorter vascular paths, especially in those passing through the viscera in which a free circulation must be steadily maintained if the metabolism is to proceed normally, the increase in the minute volume of the heart may be all the more easily secured. Although it may be that the doctrine of reciprocal innervation of the periphery and the deeper parts cannot now be maintained in any very thoroughgoing fashion, there is no question that reciprocal relations can and do exist. The relatively low blood pressure, in many of these cases, shows, in so far as it does not depend upon cardiac weakness, that the vasomotor block is not universal. Where the total

volume of the blood is increased, as in chlorosis, the increased minute volume of the heart necessitated by the deficiency in haemoglobin may be obtained with little if any diminution in the flow through the skin. For example, if the blood volume were doubled and the haemoglobin percentage halved, the total haemoglobin would be unaltered. It might then be possible that without diminution in the flow through the peripheral parts, the flow through the lungs could be doubled and the oxygen requirement completely met. In this case the quantity of haemoglobin passing through the hand, per unit of time, might be reduced to one-half without change in the blood flow, while the quantity of haemoglobin passing through the lungs would remain normal. In E. D., for example, the haemoglobin passing through 100 c.c. of hand per minute would correspond only to that contained in three grammes of normal blood, a very marked deficiency in the haemoglobin circulation through the hands for a girl of 16. In O. L., also, the apparently fair flow of about seven grammes of blood per 100 cubic centimeters of hand corresponds to the haemoglobin of only about three grammes of blood normally rich in haemoglobin.

In Mrs. A. P., whose hand blood flow appears to be normal (8.4 grammes per 100 cubic centimeters per minute for the average of the two hands), the haemoglobin going through 100 c.c. of hand per minute is equivalent only to that contained in about six grammes of normal blood, a distinct although a not very great deficiency.

We shall not discuss the question whether an increase in the minute volume of the heart in the anæmias is not obtained in part or chiefly by an acceleration in its rate. For an increase in minute volume occasioned in this way would equally affect the peripheral circulation unless a redistribution of the blood were brought about by vasmotor action in the manner already suggested. Besides, considerable difference of opinion exists among observers as to the effect of changes in the rate of the heart on its output, and as to the changes in the output which are possible.

A glance at Table II (pages 123, 124) in which the results in

the cases of anaemia are summarized, shows clearly that there is no direct relation between the pulse rate and the blood flow through the hand. The highest pulse rate of the series, 120 in H. W., was associated with one of the lowest hand flows, the lowest pulse rate, 52 in J. B., with a fair although subnormal flow. The independence of the hand flow and the pulse rate in different cases is still better displayed in Table III (page 125), embodying the results on a case of bradycardia, a case diagnosed as paroxysmal tachycardia, a case showing jaundice with a slow pulse, and a case showing jaundice with normal or somewhat accelerated pulse rate.

In the first blood flow examination in the case of bradycardia, X., with a pulse rate of 35 the flow was 10.37 grammes per 100 cubic centimeters per minute in the right hand, and 10.93 grammes in the left hand, with a room temperature of 24.7° C. A week later, with a somewhat higher average pulse rate and a room temperature of 24.5° C., the flows were respectively 8.75 grammes and 8.32 grammes. On the first day he had in accordance with his usual custom for some time taken no lunch, and had rested for a while after coming to the hospital. On the second day he had had lunch and was examined immediately on his arrival. The case was one of true bradycardia, not of heart block, the jugular tracing showing a number of *a* waves equal to the number of beats in the radial artery.

In Table III is next shown a case, F. R., a woman aged 52, with a pulse rate of 156 and a blood blow of only 4.78 grammes per 100 cubic centimeters per minute for the right hand, and 4.30 grammes for the left, although the room temperature was 26° C. This pulse rate indicates complete or almost complete inactivity of the inhibitory mechanism. It is of interest as a sign of concomitant inactivity, as regards reflex changes, of the vasomotor centres that the flow in one hand is practically unaffected by the application of heat or cold to the contralateral hand. So slight a reflex effect as that witnessed in this patient is seldom seen.

The third case in Table III, G. V., a man 44 years old, with

long-standing jaundice (8 years) and a pulse rate of 63, had a flow in the right hand of only 2.69 grammes per 100 cubic centimeters per minute, and in the left 2.62 grammes, with room temperature 22.1° C. Anæmia was probably a factor in the small peripheral flow. His hands were always cold to the touch. Whether the continued itching of the skin of which he complained was concerned in the vasoconstriction is unknown.

In S. L., a case of jaundice (diagnosis, hypertrophic biliary cirrhosis) with a normal pulse rate, or perhaps a rate somewhat accelerated, the flow in the hands was even greater than normal for the room temperature of 21.7° C.—14.86 grammes per 100 cubic centimeters per minute for the right hand, and 14.78 grammes for the left. An increase in the hand flow in disease is much less common than a decrease. The vasomotor reflexes were marked. The increased vasodilatation in the right hand (whose blood-vessels must have been already considerably dilated) on immersing the left hand in warm water is especially notable. The flow increased to 15.63 grammes per 100 cubic centimeters per minute. Immersion of the left hand in cold water caused a transient diminution of the flow in the right (to 9.05 grammes for the first two minutes), followed by an increase to 14.14 grammes per 100 cubic centimeters per minute for the remaining eight minutes of immersion.

In concluding this section of the lecture it is worth pointing out, perhaps, that if in anæmia peripheral vasoconstriction, especially in the cutaneous vessels, is a compensatory mechanism for increasing the stream of blood in the lungs, disorders of the skin caused or perpetuated by deficient circulation are rationally treated by measures which augment the haemoglobin content of the blood. When the deficiency of haemoglobin is remedied the deficiency in the cutaneous blood flow will take care of itself. It has long been known and is a commonplace of practice that many skin conditions are benefited by general treatment of the co-existing anæmia where local treatment alone is ineffectual. Local treatment of limited portions of the skin, however, aimed at increasing the blood flow there, would not be contraindicated from the point of view of the compensatory action of a general

peripheral vasoconstriction. For vasodilatation in a limited area of the skin, while it might greatly benefit the local condition, would not appreciably affect the pulmonary flow.

In one and the same healthy individual and in pathological cases where the clinical state has undergone no sensible change, the hand flow varies only within narrow limits when the subject is under a steady regimen, and the controllable external conditions are the same. Where anæmia fever (p. 122) and possibly some other conditions (p. 148) are excluded it is probable that the hand flow is an index to the minute volume of the heart, and gives the means in successive observations of following to some extent changes in the minute volume. When the hand flow is not below the normal we can almost always conclude that the heart output is not less than normal (p. 133). The fact then that X., with a pulse rate of 35, had a hand flow entirely within the normal range for his age may be taken to indicate that his minute volume under the given external conditions was not less than normal. The output per beat must, therefore, have been twice that of a normal man of the same weight. Nothing, of course, can be said from these observations as to the power of his heart to respond to such increased requirements as occur during considerable muscular exertion. Miss Buchanan has remarked that among athletes at Oxford (rowing men) very slow pulse rates are not incompatible with great physical exertion.

CONCLUSIONS OF SECTION IV

1. In the cases of anæmia studied (pernicious anæmia, chlorosis, and secondary anæmia) the blood flow in the hand is smaller than the normal flow.
2. Accepting Plesch's result, that the minute volume of the heart is increased in the anæmias, the diminution in the hand flow is interpreted as a token of a vasoconstriction in peripheral parts which facilitates the increased flow through the lungs.
3. The deficiency in the hand flow is less in the chlorotic group than in the other cases of anæmia. The explanation suggested is that the increased total volume of the blood in chlorosis

permits the normal amount of haemoglobin to circulate through the lungs without entailing a marked increase in the vasoconstriction of the peripheral parts.

4. The view that the diminution in the cutaneous blood flow in anaemia is a necessary compensatory arrangement for increasing the flow through the lungs affords a natural explanation of the beneficial effect in many cutaneous disorders of general measures, especially those aimed at improving the quality of the blood.

5. In a case of bradycardia with a pulse rate permanently below 40 during rest in a sitting position, the hand flow was normal.

SECTION V. THE BLOOD FLOW (MAINLY IN THE FEET) IN FEVER

In spite of much discussion we possess but little exact knowledge of the changes in the cutaneous circulation in fever, which constitute an essential, probably the chief, factor in the derangement of the temperature-regulating mechanism. I have endeavored to make a small contribution to our data by measuring approximately the blood flow in the feet in a number of cases of typhoid fever and in one case of pneumonia. Of one of the cases of typhoid four examinations were made in the course of a month. In a second case a similar program was planned but had to be modified on account of hemorrhage, and only two examinations were carried out. These, however, happened to be at the most interesting stages in the course of the fever. For comparison three cases at different stages in convalescence were investigated, each on one occasion. In the pneumonia case two examinations were secured, the last one four days before the death of the patient. The first of the typhoid patients, F. D., was far enough advanced in convalescence to permit him to sit up in a chair for the examination of the hands.

Here the hand flow lies within the normal range, being 9.16 grammes per 100 cubic centimeters per minute for the right hand, and 8.63 grammes for the left, with room temperature 23° C. The foot flow is much below the normal (0.98 grammes

TABLE II.

Case.	Age in yrs.	Date.	Pulse rate.	Blood pressure.	Temperature (C.) of		Hand volume in c.c.	Heat given off in small calories.	Blood flow in gm. per min.	Flow per 100 gm. of hand per min.	Notes.								
					Room.	Arterial blood.	Right.	Left.	Right.	Left.									
H. W.	24	April 18, 1911	120		23.5	30.19	30.20	41.2	378	931	753	17	8.49	6.88	2.06	1.82	Pernicious anæmia.		
D. K.	44	July 2, 1912	84	103, (82) 60	29.1	37.7	32.05	32.03	480	476	3,670	3,667	18	40.09	39.92	8.35	8.38	Pernicious anæmia.	
S. K.	48	Jan. 24, 1913	108		29.2	32.54	32.67			191	957	7	13.70	2.85	Left hand in cold water.				
F. W.	22	Dec. 27, 1912	100	124, 73	24.7	36.75	31.55	31.45	449	403	1,589	1,145	15	22.63	16.00	5.04	3.94	Hæmophilia.	
Mrs. M. A.	38	Jan. 28, 1913	80	118, (85), 130	24.2	31.80				1,126	1,031	1,296	11	22.97	5.11	Left hand in warm water.			
E. D.	16	Feb. 5, 1912	96	105, (85) 73	22.2	37.0	31.21	31.19	303	275	1,285	1,077	13	18.96	15.84	6.25	5.76	Left hand in cold water.	
Mrs. A. P.	32	Feb. 4, 1913	104	115, 63	23.5	37.0	31.12	31.03	390	386	1,806	1,678	10	34.12	31.23	8.75	8.09	Hæmoglobin 80.	
Mrs. T.	30	Jan. 11, 1911	72	22.6	37.6	30.58	30.55	275	245	1,466	1,456	13	17.84	17.65	6.48	7.20	Hæmoglobin 50.		

¹ The numbers in parentheses are the pressures determined by the auscultatory method at which the abrupt decline in the sound occurred, the smaller numbers following are the pressures at which the sound disappeared.

TABLE II.—Continued.

TABLE III.

Case.	Age in yrs.	Date.	Pulse rate.	Blood pressure.	Temperature (C.) of		Hand volume in c.c.	Heat given off in small calories.	Blood flow per 100 c.c. of hand per min.	Notes.								
					Arterial	Blood	Right.	Left.	Right.	Left.								
X.	32	Juns 4, 1912 ³⁵			24.7	36.7	31.62	31.60	493	469	3,506	3,531	15	51.12	51.28	10.37	10.93	After rest. No lunch.
		June 11, 1912 ^{31,35}			24.5	37.0	31.60	31.47	477	444	3,650	3,312	18	41.72	36.97	8.75	8.32	After lunch, without rest.
Mrs. F. R.	52	May 25, 1911 ¹⁵⁶			26.0	38.1	30.12	30.03	326	335	1,007	942	9	15.58	14.41	4.78	4.30	Left hand in warm water.
							30.35		940		8	16.84		5.16				
G. V.	44	Sept. 27, 1912 ⁶³	105.69	22.1	37.1	31.04	30.98	473	467	1,320	1,284	19	12.73	12.27	2.69	2.62	Left hand in cold water.	
S. L.	35	Jan. 8, 1913 ⁸⁴	117, (100) 80	21.7	36.75	31.77	31.69	494	467	4,938	4,718	15	73.45	69.06	14.86	14.78	Left hand in cold water.	
				22.4	32.40				350	2	44.70		9.05					
					22.2	32.66				2,058	8	63.88		14.14				
					22.1	33.16				2,495	10	77.22		15.63				

per 100 cubic centimeters per minute for the right, and 0.85 grammes for the left). The ratio of the combined foot flows to the combined hand flows (1 to 9.7) is much too small and indicates clearly an abnormal sensitiveness of the feet to vasoconstriction, the exciting cause being probably the necessary exposure of the feet to the air and water. We shall see that there is evidence in the foot flows of abnormally great cutaneous vasoconstriction in all the typhoid cases examined, and at all stages of the fever which happened to coincide with an examination. This tendency to vasoconstriction seems to be carried into convalescence.

In the case of J. McD., who was still further advanced in convalescence than F. D., the prolonged reflex vasoconstriction, not followed by any vasodilatation in the left hand when the right was immersed in warm water, might be interpreted in the same way, as also the marked inferiority of the flow in the right hand as compared with the left. Such differences between the two hands in the absence of any known anatomical cause are apt to be observed in persons who exhibit other evidences of nervous, including vasomotor, instability.

Hyperexcitability of the vasoconstrictor mechanisms of the periphery is most naturally interpreted as a defensive reaction of the organism by which an increased supply of blood is afforded for those internal organs which bear the brunt of the infection. The fact that the blood pressure is low and the pulse dicrotic in spite of the constriction of the vessels of the periphery, indicates that other vascular paths, especially the splanchnic area, are more widely opened than usual. The fever, the rise of temperature of the internal parts and of the blood, may be considered as, in the main, a secondary and inevitable, and perhaps in itself an unimportant consequence of a sustained cutaneous vasoconstriction. When the temperature has risen to a certain height a balance between heat production and heat loss is necessarily again reached in spite of the vasoconstriction. Indeed, were the circulation in the skin entirely stopped it is clear that such a balance must also be eventually reached by augmentation of the flow of heat by conduction from the deeper parts.

It must be remembered that with a normal flow through the skin in fever the amount of heat given off would be greater than normal on account of the higher temperature of the blood. Table IV illustrates this point. Thus, while the amount of heat given off per 100 cubic centimeters of foot per minute in all the fever cases does not rise beyond the range for the normal

TABLE IV.

Case.	Date.	Heat given off per min. in small calories.		Heat given off per 100 c.c. of foot per min.		Heat given off per gm. of blood.		Rectal temperature. C.
		Right.	Left.	Right.	Left.	Right.	Left.	
Normal Individuals.								
M. C.	May 2, 1911	251.6	—	20.6	—	5.77	—	37.4
	May 18, 1911	211.6	—	17.4	—	4.93	—	37.5
	June 17, 1911	332.3	278.8	28.4	25.6	5.76	6.06	37.6
	Mar. 26, 1913	290.2	290.2	23.5	24.2	4.60	4.64	37.1
	May 2, 1911	262.1	—	26.7	—	5.65	—	36.9
	Mar. 25, 1913	351.7	327.1	34.8	34.1	4.37	4.49	37.0
N. R.	Apr. 8, 1913	83.8	70.6	17.0	14.7	5.05	5.14	37.2
Fever Patients.								
F. B.	Dec. 5, 1912	145.0	151.5	13.4	14.5	6.41	6.29	39.4
	Dec. 11, 1912	98.0	78.4	9.1	7.6	6.69	6.83	39.3
J. B.	Oct. 2, 1912	211.3	240.0	22.7	25.3	6.78	6.63	39.35
	Oct. 16, 1912	54.7	50.2	6.5	6.0	8.18	8.12	40.2
M. V.	Nov. 1, 1912	95.7	81.6	12.2	11.0	5.87	5.81	37.45
	Oct. 8, 1912	163.0	157.9	12.3	12.2	8.00	8.13	40.5
F. S.	Nov. 5, 1912	81.8	90.8	7.3	8.2	5.91	5.87	37.95
	Oct. 2, 1912	94.7	90.2	7.3	7.1	4.97	5.13	37.9
F. D.	Oct. 1, 1912	56.8	49.1	4.1	4.3	5.12	5.19	37.2

persons, the amount of heat given off per gramme of blood passing through the foot is much greater in fever than with normal body temperature. And it is precisely when the flow of blood is small and the rectal temperature high that the heat loss per gramme of blood is greatest. Thus in J. B. on October 16, 1912, with rectal temperature 40.2° C., and in M. V. on October 8, 1912, with rectal temperature 40.5° C., over eight small

(gramme) calories per gramme of blood are given off to the calorimeters, whereas the corresponding number for a normal person is always below six for the average of the two feet. The difference does not depend upon variations in the calorimeter temperatures in the different experiments. It is essential to point this out, as it is obvious that it is inherent in the method that the lower the calorimeter temperature the greater must be the heat loss per gramme of blood passing through the part. The slight differences in the heat given off by the two hands or by the two feet in one and the same experiment depend upon differences in the calorimeter temperatures.

If the cutaneous vasoconstriction is in the interests of an increase in the blood flow to the organs on which the stress of the infection falls, it is plain that if the increased temperature is to be combated by direct measures the most rational procedure is to hasten the loss of heat without dilatation of the skin vessels, or still better while their constriction is even increased. This indication is admirably met by the cold bath treatment. On the other hand, the use of antipyretics which act by causing cutaneous vasodilatation would seem to be unphysiological, since in diminishing the temperature they cause the withdrawal of blood from the seats of infection.

M. V. was examined for the first time on the day following his admission to the hospital. His rectal temperature was 40.5° C. (104.9° F.), although he had had a full bath two hours before the examination. The flow was only 1.54 grammes per 100 cubic centimeters of foot per minute for the right foot, and 1.50 grammes for the left, with room temperature 22.2° C. On account of hemorrhage nine days after the first examination, it was not considered justifiable to carry out the original program, since, although the examination caused apparently very little disturbance to the patient, absolute rest was obviously enjoined in his case. Accordingly an interval of exactly four weeks elapsed between the first and the second examination of the blood flow. His rectal temperature at the second examination was 37.95° C. (100.3° F.). The foot flow was somewhat smaller than at the first examination (1.24 grammes per 100 cubic centi-

meters per minute for the right, and 1.40 grames for the left, with room temperature 22.9°). Of course the amount of heat given off per minute to the calorimeter was much greater at the first examination than at the second on account of the higher blood temperature. This renders it necessary to state that it has not hitherto been feasible to determine by actual experiment in a fever case the relation between the rectal temperature and the temperature of the arterial blood at the ankle under the average conditions of our blood flow observations. It has been assumed in the calculations that the difference is 0.6° C., the same as for a normal person. It is, of course, possible that in fever the temperature of the blood as it passes from the heart to the wrist or ankle falls more than in health, since the excess of temperature of the skin over that of the surroundings is greater. Yet the arterial blood moves so rapidly and the large arteries are so well protected that it can scarcely be supposed that any considerable difference exists. It must be taken into account also that in the observations the limbs were covered as far as possible down to the calorimeters. It may therefore be confidently assumed that the calculations are not vitiated in any important degree by the want of direct experimental control of this factor.

The greatest number of observations were obtained on J. B. The first examination of J. B. was made on October 2, 1912, ten days after his admission, more than four weeks from the beginning of his illness, and a week after the maximum temperature (105.8° F.) had been reached. The rectal temperature after the examination was 39.35° C. (102.83° F.). The flow in the feet was the largest observed in this series of fever cases and the only flow which fell within the normal range (viz.: 3.36 grammes per 100 cubic centimeters per minute for the right foot, and 3.82 grammes for the left, with room temperature 24.4° C.).

Six days later, his temperature having meanwhile mounted again and continued high, the foot flow was found to be much smaller and eight days later, on October 16, the rectal temperature being now 40.2° C. (104.36° F.), the flow was only 0.80 gramme for the right foot and 0.74 gramme for the left. The

clinical records show great variations in temperature since the first examination and he continued to present disturbing cardiac and other symptoms.

The last examination was made on November 1, 1912, almost seven weeks after admission to the hospital and ten weeks after the beginning of the illness, his temperature being now for the first time fairly stable and at a normal level. The flow was 2.08 grammes per 100 cubic centimeters per minute for the right foot and 1.89 grammes for the left. In view of the fact that the room temperature was more than 2° C. lower on this than on the first occasion, the results indicate that at the first examination the conditions that determine the rate of flow in the feet were more similar to the conditions at the last examination than to those at the two intermediate examinations, in spite of the great difference of body temperature. The most natural explanation is that both at the first and the last examination in this rather protracted case the intoxication was subsiding and the cutaneous vasoconstriction was disappearing. After the first examination, however, a relapse seems to have occurred, the patient's progress being interrupted by complicating incidents (continued ulceration, etc.), the cutaneous vasoconstriction increased, and the temperature ran up again almost, if not quite, to the maximum reached before. In the absence of simultaneous measurements of the hand flow it is impossible to know whether intoxication of the heart contributed to the smallness of the foot flows in the intermediate period, although from the heart symptoms this seems probable. The progressive diminution in the volume of the feet in the first three examinations is a point which may be noted, since it affords a quantitative expression (for a particular part) of the increasing emaciation which was very evident in the body as a whole. The foot volume at the fourth examination is not comparable with the others, as the reduced calorimeters were then used for the first time.

In F. B., a case of pneumonia, the flow at the first examination, on the day of his admission to the hospital and a fortnight from the beginning of his illness, was 2.07

grammes per 100 cubic centimeters of foot per minute for the right foot, and 2.30 grammes for the left, with room temperature 23.0° C.,—flows not perhaps markedly deficient for his age, but certainly not above the normal. Six days later the flow was less (1.36 grammes for the right, and 1.12 grammes for the left foot) with a slightly lower room temperature, but practically the same rectal temperature. Here again in the absence of observations on the hands it cannot be stated what share the weakening of the heart might have had in the diminution of the flow. That it was weakening at this time is probable, as he died four and a half days later, apparently from a general intoxication.

CONCLUSIONS OF SECTION V

1. In the cases of fever investigated the flow in the feet never exceeded the normal flow and was usually much below the normal.

2. In explanation of the relatively small foot flow in the fever cases it is suggested that the vasoconstrictor mechanism of the peripheral parts, especially of the skin, is abnormally excited, and some direct evidence that this is the case is brought forward.

3. The significance of this hypersensitiveness, or at least increased action, of the cutaneous vasoconstrictor mechanism is assumed to be that the peripheral vasoconstriction is a compensatory arrangement which secures for the organs mainly suffering from the infective process an increased flow of blood.

4. On this hypothesis the rise of temperature is, chiefly at least, secondary, inevitably following the vasoconstriction, provided that the metabolism is, upon the whole, not diminished.

5. Accordingly the rational treatment of hyperpyrexia, or of pyrexia if it is considered necessary to treat it, is to abstract heat by a process which will not diminish and may even increase the cutaneous vasoconstriction. This condition is exactly fulfilled by the cold bath, at least as regards its initial effect. Other so-called tonic effects of the cold bath are not considered here.

Antipyretic drugs which act by dilating the cutaneous vessels would seem to be inferior in this regard. They diminish the temperature, it is true, but at the cost of defeating the beneficial redistribution of the blood which it is the function of the peripheral vasoconstriction to insure.

6. It is obvious that for the elimination of a given quantity of heat from the skin by radiation and conduction * in fever, a smaller cutaneous blood flow will suffice than with normal body temperature, since the elimination of heat per gramme of blood passing through the surface must be greater in fever owing to the greater difference of temperature between the surface of the body and its surroundings.

I am much indebted to the staff of the City Hospital for their coöperation which has rendered this investigation possible.

As the paper is already unduly long only general summaries of the results in the remaining sections will be given without reference to details of the separate measurements.

SECTION VI. DISEASES OF THE HEART

A few words are necessary in regard to the classification of the cases dealt with in this section. Some overlapping between the groups is unavoidable and the attempt has been made to assign each case presenting a complication of lesions to the group in which the factor seemingly predominant in the clinical picture in so far as light can be thrown upon this by the blood flow measurements would place it. For example, in the group of myocardial affections, cases are necessarily included in which there were very definite and demonstrable valvular lesions, *e.g.*, three cases of mitral stenosis (and insufficiency) in which there was evidence that auricular fibrillation was also present, and that probably this condition with the consequent marked disturbance of the action of the ventricle was, at the time of the investigation at least, a more important factor in the clinical situation than the valvular lesion or at least a factor which

* Loss of heat by sweat is not considered, since the parts investigated could not lose heat in this way under the conditions of the observations.

differentiated the cases from others with the valvular lesion alone, and lent to them an added gravity.

In comparing the flows in the whole series of cases investigated with those in normal persons, one is struck by the fact that while in persons suffering from well characterized pathological changes (compensated valvular lesions, for example) the flow may be of the normal magnitude having regard to the age of the patient, the room temperature, and similar conditions, in a larger number of cases it is below the normal, often greatly below it. Sometimes there is good evidence that this diminution in the hand or foot flow is the expression of an increased excitability of the vasoconstrictor mechanism as a whole or at least of the portion of it which presides over the cutaneous vessels not necessarily related to any material diminution in the driving power or the output of the heart. In other cases there is evidence that the diminished flow in the hand (or foot) is in the main the expression of diminished functional capacity on the part of the heart, and associated either with engorgement of the veins and the right side of the heart or with diminution in the filling of the arteries without increased venous pressure.

The question, under what condition the flow in the hands or feet is an indication of the functional capacity of the heart, may be answered provisionally here. Where the hand (and foot) flow is not less than normal it is only in quite exceptional conditions (local vasomotor paralysis of hands and feet?) that any error will be made in assuming that the heart is discharging an amount of blood not inferior to the normal. When, however, the flow in the extremities is permanently and decidedly less than normal several points have to be considered. In many of these cases where the normal ratio of the hand to the foot flow is preserved (see Paper VII of the series, *Journal of Experimental Medicine*, 1913, xviii, p. 354), in spite of the diminution in the flow and where no anæmia is present, there is often reason to believe that the lessened driving power of the heart is primarily responsible for the diminished flow. On the other hand, in the anæmias (Paper VI of the series, *Journal of*

Experimental Medicine, 1913, xviii, No. 2) the diminution of the flow in the hand and in the skin generally seems to be a compensating mechanism which permits an even increased quantity of blood to be sent by the heart through the lungs.

SUMMARY

1. The smallest flows observed in the series of cases dealt with in this section have been associated with marked irregularity of the heart, indicating involvement of the mechanism of the heart beat. In some of these cases the cardiac irregularity was associated with valvular lesions, but in those with the very smallest hand flows there was no evidence that the valves were involved.

2. Three cases were diagnosed as auricular fibrillation, all associated with mitral stenosis and insufficiency. While the flow in all was below the normal it was decidedly greater in one patient than in the other two, in spite of his being much the oldest of the three. This corresponded well with his clinical condition, which was good at the time of the examination. The ventricle in spite of its extremely irregular action was upon the whole beating fairly strongly, and was obviously delivering a fair amount of blood to the periphery. On the other hand the patient with the smallest hand flow complained that she was always cold.

3. In a case of mitral stenosis and insufficiency and tricuspid insufficiency in which the heart showed marked arrhythmia in part associated with the respiration, the hand flow was also much below the normal sinus arrhythmia.

4. Abnormally small flows have also been seen in a number of cases diagnosed as myocarditis with regular action of the heart, but feeble heart sounds not accompanied by murmurs.

5. In a certain number of cases diagnosed as myocarditis without valvular lesion in which a serious clinical condition had previously existed, very fair hand flows, not much inferior to the normal, were found when the clinical condition had markedly improved.

6. In several cases of mitral insufficiency with good com-

pensation and no signs of impairment of the myocardium the hand flow was found to be quite up to the normal amount. In one case of mitral stenosis and insufficiency the flow appeared to be even somewhat greater than normal, as if the big, well-compensated heart was discharging even more than the usual quantity of blood.

7. In a case of apparently pure aortic stenosis with seemingly perfect compensation, the hand flow was normal.

8. In two cases of mitral insufficiency with badly broken compensation with venous engorgement, oedema, cyanosis and dyspnoea, the hand flow was much below the normal. In one of these cases a striking diminution occurred a few days before death.

9. In a case of mitral insufficiency with broken compensation, venous engorgement and oedema, but no dyspnoea or cyanosis, the hand flow was quite up to normal. In another case with the same lesions where there was little oedema, no shortness of breath except on exertion and none at the time of examination, the flow was also little if at all inferior to the normal flow, and the restoration of compensation was associated with an actual moderate diminution in the flow.

10. In a case of aortic insufficiency and stenosis, with badly broken compensation (great dyspnoea, pulmonary oedema), the hand flow was greatly diminished. In another case of aortic stenosis and insufficiency with mitral insufficiency, while there were no signs of broken compensation the hand flow was somewhat below the normal.

11. In a case of mitral insufficiency with physical signs of pericardial effusion a flow not much inferior to the normal was found after the patient had been some time in the hospital and had regained compensation and when the heart dulness had decidedly diminished. Two days after leaving the hospital he broke down again and returned with some dyspnoea, cough and swelling of the legs. The hand flow was now found distinctly below its previous value.

While it is obvious that some of the groups of cases are much better represented in the observations than others, as is

easily understood from the fact that they had to be collected as chance offered, certain general conclusions which, although of course at present only provisional, are yet entitled to some weight, seem to emerge with sufficient clearness. It is scarcely necessary to say that in some points these conclusions simply confirm what is found by palpation of the radial pulse. But it is by no means the case that even the qualitative result of the blood flow measurement can always be predicted from feeling the pulse.

I. The hand flow is far more apt to be markedly deficient in cases where there is evidence of serious impairment of the myocardium, or more comprehensively and probably more accurately of the mechanisms on which the force and rhythm of the heart's action depend, even when valvular lesions are absent, than in cases where gross valvular lesions exist while the heart's action is strong and orderly. With a heart whose myocardium is seriously crippled, even when the valves are anatomically and probably functionally intact, the hand flow may sink to astonishingly small figures. Nor is this difficult to understand. A pump with somewhat leaky valves may still deliver a good stream when the strokes are strong and regular. No matter how tight the valves are the output will be small if the stroke is feeble, uncertain and irregular. This broad distinction holds even when in cases of valvular disease the clinical signs of loss of compensation are evident. It seems, however, to be less true of aortic insufficiency than of mitral insufficiency. In aortic insufficiency the hand flow appears to be less easily maintained at the normal level and to fall below it more readily when compensation is lost than in mitral insufficiency.

II. Even where there is considerable venous engorgement in cardiac cases the flow in the hands may be little if at all diminished provided that the myocardium is not impaired. A marked diminution in the hand flow in a case of valvular lesion with great engorgement of the veins where the initial hand flow was already distinctly subnormal, appears to indicate failure of the myocardium. On the other hand when in a case of broken compensation the flow in the hand is even above the

normal the re-establishment of compensation may be associated with a moderate decline.

III. When in a cardiac case with broken compensation the hand flow is normal or not much diminished the indication is that the myocardium as yet has not suffered serious impairment. A decided diminution in the course of the case may be significant of impending failure of the myocardium.

SECTION VII. CERTAIN VASCULAR CONDITIONS

1. Arteriosclerosis.

It need scarcely be mentioned that several of the cases included in the previous section, in addition to valvular lesions of the heart or myocardial changes, suffered from arteriosclerosis. In this section a few cases were studied in which arteriosclerosis was marked and other lesions, if present, did not dominate the clinical picture. As a general result of the observations it may be stated that in marked arteriosclerosis the flow in the hands is always smaller and the vasomotor reflexes weaker than in normal persons. Vasodilatation is easier to obtain by the application of warmth to the contralateral hand than vasoconstriction by the application of cold.

2. Thoracic aneurism.

For the age of the patients and the temperature of the room the hand flows in the cases of thoracic aneurism examined were either of the normal order of magnitude or at least not so conspicuously deficient as in cases where the stress of the pathological change falls upon the myocardium rather than on the blood-vessels. It is not of course suggested that in some of the cases of aneurism deterioration and disordered function of the myocardium may not be of graver import than the aneurism itself. But in so far as the aneurism, or rather the underlying condition which has occasioned the aneurism, has not led to deterioration of the heart, there is no reason in the mechanics of the circulation why the blood flow through the hand should suffer. This is true even where the form of the pulse wave may be greatly distorted by the presence of the aneurismal sac. For example, in a man 31 years old, suffering

from aneurism of the arch of the aorta, very marked differences in the radial pulse on the two sides, differences perfectly evident both to the finger and on the sphygmogram, were associated with equality of the flow between the two hands. The right radial showed a typical pulse of aortic insufficiency with abrupt ascent to a sharp apex and abrupt fall, while the left radial gave a sphygmogram with a rounded apex. The blood pressure in the two brachials was also quite different, the systolic pressure being 157 in the right, and 118 in the left. Three days previously the pressures were 160 (systolic), 45 (change of sound) in the right, and 130, 55 in the left brachial. There was liquid in the left pleural cavity and the physical signs of aortic insufficiency were present.

The blood flow measurement showed an almost absolute equality between the two hands (11.11 grammes per 100 c.c. per minute for the right, and 11.06 grammes for the left with room temperature 23.2°), a perfectly normal flow for a man of this age. The conclusion was drawn that the aneurism in distorting the form of the pulse wave did not interfere with the free passage of blood through the left subclavian artery, and this was confirmed, it is believed, by the necropsy findings. The man died the same night, about 10 hours after the examination, by a rupture of the aneurism into the left bronchus. It is worthy of remark that 10 hours before his death the blood flow in his hands, which no doubt in this case was an index of the output of his heart, was quite normal, although this is of course what was to be expected. He was to die not because his heart was failing but because the wall of the aneurismal sac had been thinned to the bursting point. A very different tale would have been told by the hand flow in a case of impending heart failure.

Of course a sufficient degree of pressure of the sac on a subclavian artery or vein may diminish the flow in the corresponding hand. Yet a distinct unilateral distention of the veins is compatible not only with equality of the flow in the two hands, but even with a preponderance on the side of the distention if other circumstances more than compensate for the

increased venous pressure. Thus in a man aged 38 years, with a spherical aneurism of the innominate (as shown by necropsy), with venous obstruction on the right side, there was a decided deficiency in the flow of the left hand as compared with the right (10.91 grammes per 100 c.c. per minute for the right, 8.15 grammes for the left, a ratio of 1.33:1). For the room temperature of 28° C., 10.9 grammes is not a large flow, but neither is it decidedly small. The vasomotor reflexes from the right to the left hand were normal in direction, and not strikingly deficient in intensity, showing that the chief afferent paths in the vasomotor reaction to warmth or cold (the nerves of warmth and cold sensation) have not appreciably suffered by stagnation of the circulation due to the pressure of the aneurism on the subclavian vein. Now when pressure is maintained on the arm at a level somewhat below the systolic arterial pressure by means of the cuff of a sphygmometer the warmth sensations suffer early so that it is impossible to appreciate the contact of a warm tube while the sensation of pain is at this stage less affected. As has been pointed out in Paper X of the series (Archives of Internal Medicine, 1913), a certain amount of venous distention, provided that the arterial pressure is correspondingly increased, may even be associated with an increased flow, because of the increased cross-section of the smaller vessels. So far as the arterial path to the right arm is concerned, the conditions would favor a greater flow in the right hand, for as shown at the necropsy the aneurism provides a much wider entrance than normal for the blood going to the right subclavian and possibly a reservoir which helps to maintain the flow during diastole.

3. Miscellaneous vascular conditions, including vascular neuroses.

Among these were three cases of typical Raynaud's disease. In all the flow was small, the diminution being in proportion to the length of time for which the condition had existed. In the earlier cases the contralateral vasomotor reaction to cold was peculiarly intense. In the case of longest standing (8 years) which had gone on to gangrene this reaction was missed

probably because of permanent anatomical changes in the vessels and their nerves. In all three cases some general enfeeblement of the circulation seemed to be the background on which the local condition projected itself, since improvement in the general condition, in the earlier stages at least, appeared to be followed by diminution in the frequency and severity of the local attacks.

In a case of dead fingers in an elderly man affecting only the right hand the flows were among the smallest observed in the whole investigation and this not only in the hand obviously affected but also in the other. A fair reflex vasodilatation was obtained in the right hand on the immersion of the left in warm water. The dead condition of the right hand is therefore probably not due to anatomical change in the vessels but to a vasoconstriction.

In a case of diabetic gangrene of the feet more advanced in the left than in the right in a man 63 years old, the flow with a room temperature of 25.6° C. was 1.39 grammes for the right foot and 1.83 grammes for the left, or, allowing for the swelling of the latter, 1.95 grammes. The hand flow was 2.65 grammes for the right hand and 3.32 grammes for the left per 100 c.c. per minute with room temperature 22.0° C. The fact that the flow both in the hands and feet is decidedly below the normal agrees with the well-known feebleness of the cutaneous circulation in diabetes and is probably in part due to cardiac changes, since the ratio of foot to hand flow lies within the normal range. The vasomotor reflex when warm water is applied to the contralateral hand is very poor. Whether this indicates the beginning of pathological changes in the hand arteries also cannot of course be definitely stated. It is in any case interesting to correlate the enfeeblement of this vasomotor reflex with the enfeeblement or disappearance of skeletal reflexes such as the knee jerk, which is known to occur in long-standing cases.

In a case of gangrene of the toes of the left foot of doubtful etiology the flow was 2.15 grammes per 100 c.c. per minute in the right foot and in the left foot 3.42 grammes.

The question whether the gangrene was going to spread was what chiefly interested the physician in charge of the case. The fact that the flow in the feet was so good was interpreted as favorable for the prognosis, although of course it was impossible to say to what extent the flow in the toes themselves had been interfered with. The left foot was somewhat swollen, as shown by the volume measurement. Yet it was only a little over 3 per cent. larger than the right. The greater flow in the left was probably associated with a certain degree of inflammatory reaction. The foot soon healed to a considerable extent.

It was afterward ascertained that the man had frozen his feet the previous winter. The local condition, however, was associated with myocarditis and general cyanosis, the hand flow was extremely small, and the patient eventually died.

The last case to be mentioned in this section is that of a man with local oedema and cyanosis of the right foot and leg which comes on with great rapidity in the standing position and rapidly disappears when he lies down. There was anaesthesia in the affected region and the distribution of the anaesthesia and the history of the case seemed to indicate that a nerve injury was the starting point of the vascular condition. The flow in the right foot was 0.51 grammes per 100 c.c. per minute and in the left 1.35 grammes with room temperature 23.0° C. The flow in the right hand was 3.43 grammes, and in the left hand 3.71 grammes per 100 c.c. per minute with room temperature 22.6° C. While, then, the flow in the hands is much below the normal, which corresponds well with the rather feeble action of the heart and with his anaemic condition, the flow in the left foot preserves a ratio to that in the hands not far from normal. The flow in the right foot, however, is distinctly poor, even in proportion to the poor hand flow. The cause accordingly of the small flow in the right foot is not a central one, but is local. This agrees well with his observation that he cannot keep the right foot warm and that the red color which it first exhibits when he stands soon becomes pale blue. The blood flow measurement corroborates the conclusion that

in the right foot the blood is stagnating in the capillaries of the engorged area.

SECTION VIII. DISEASES OF THE NERVOUS SYSTEM

In several cases of early peripheral neuritis confined to one upper extremity it was observed that the flow was distinctly greater on the affected than on the sound side. Thus in a brick-layer, aged 45 years, the flow on the affected (right) side was 10.29 grammes, and only 7.66 grammes per 100 c.c. per minute in the normal hand. The preponderance for the right hand is much greater than the slight excess which is usually found in right-handed individuals. The most plausible explanation is that the vasoconstrictor fibres of the hand are involved in the pathological process and are partially paralyzed. The vasomotor reaction in the affected hand to the immersion of the sound hand in cold water is prompt and strong (the flow being diminished from 10.29 grammes to 5.18 grammes), but it does not last long, and the flow soon increases (to 8.16 grammes) while the sound hand is still in the cold water.

In a case of long-standing right brachial neuritis with marked atrophy of muscles and practical disuse of the hand, the flow was found much less in the affected than in the sound hand (3.98 grammes as against 5.70 grammes). In an unusual case of post-typoidal neuritis of many years' standing, R. E., the hand which was functionally most affected had the smaller flow (Table V, pp. 144, 145). It was shown in this case and also in a case of traumatic injury to the median nerve (Table VI, pp. 146, 147) in a normal man, O. C. W., that vasomotor reflexes can be elicited by warmth and cold from regions devoid of temperature sensibility, although they are feebler than the normal reflexes. In a case of hemiplegia (cerebral hemorrhage) of nine years' standing the difference was in the same direction, the flow being 4.67 grammes in the paralyzed and 9.15 grammes in the normal hand. Absolutely no vasomotor reaction could be elicited in this case in the paralyzed hand when the sound hand was placed either in cold or warm water. The secondary changes

in the blood-vessels of the paralyzed hand and in the vasomotor endings may be supposed to constitute an effective organic block to the reflex vasomotor impulses.

In none of the cases of hemiplegia examined did the flow on the paralyzed side preponderate, while in all the cases of unilateral peripheral neuritis such preponderance existed, except in those of long standing associated with marked muscular atrophy. In tabes the flow, both in hands and feet, was found diminished and the vasomotor reflexes feeble in such cases as were examined.

In a young man recovering from tetanus after treatment with antitoxin the vasomotor reflexes were notably intense. It is unknown whether the excitability of these as well as the skeletal reflex arcs is increased by the toxin. Intense vasomotor reflexes were also observed in a case of cerebral tumor with the signs of increased intracranial pressure. It might be suggested that this was connected with an increase in the excitability of the vasomotor centre in response to the increased intracranial pressure in the interests of the blood flow through the brain.

In two cases of lead poisoning (without palsy) the tendency to reflex vasoconstriction was decided. This was also observed in several cases of alcoholic neuritis. In a case of alcoholic intoxication and in a case of excessive cigarette smoking the opposite was observed, namely, a tendency to marked reflex vasodilatation.

SECTION IX. DISEASES OF THE RESPIRATORY SYSTEM

From the relations of the lungs and pleura to the subclavian vessels it seemed possible that pulmonary lesions, especially unilateral, might produce a demonstrable inequality in the flow in the two hands. The possibility even exists that lesions of the lungs might affect the vasomotor fibres for the upper extremity on their course from the cord through the lymphatic chain, and an effect of this kind entirely or mainly unilateral might be revealed by inequality in the hand flows. Accordingly a series of chronic cases of pulmonary tuberculosis affecting chiefly one lung were examined. While no difference in the

TABLE V.
SUMMARY OF RESULTS ON R. E. (See p. 142.)

Date.	Temperature C. of			Vol. of hand in c.c.	Heat given off in small calories.	Blood flow gms. per min.	Flow per 100 c.c. of hand per min.	Notes.		
	Right.	Left.	Ar. Bl.							
April 26	24.0	30.82	30.69	36.6	379	397	951	1,469	15 12.19 18.41 3.21 4.56 For the 15 mins. preceding the vasoconstrictor test.	
	...	30.85	30.78	459	595	6 14.78 19.02 3.90 4.71 For 6 mins. immediately preceding the vasoconstrictor test.	
May 2	24.0	30.88	30.88	444	6 14.37 14.37 3.56 First 6 mins. immersion of right hand and wrist in warm water.	
	23.6	31.04	31.18	1,161	8 26.00 26.00 7.19 Next 8 minutes.	
	...	31.18	31.22	287	3 19.61 19.61 4.86 First 3 mins. with right hand and wrist in cold water.		
	...	31.22	31.22	636	12 10.94 10.94 2.71 Next 12 minutes.		
May 8	25.4	31.10	31.19	36.6	361	385	541	578	10 10.93 11.87 3.03 3.08 For 10 mins. before vasoconstrictor test.	
	25.4	31.14	31.14	237	...	5 9.64 2.67 2.67 4.03 First 5 mins. immersion of left hand in warm water.	
	24.9	31.28	31.28	1,150	...	8 30.02 30.02 8.31 Next 8 minutes.	
	25.0	31.44	31.44	271	...	2 29.18 29.18 8.08 First 2 mins. with left hand in cold water.	
	...	31.55	31.04	31.06	36.95	403	421	1,213	1,407 12 19.00 22.12 4.71 5.25 For the 12 mins. preceding vasoconstrictor test.	
	22.9	...	31.27	423	...	6 15.51 15.51 4.29 4.29 4.03 First 10 mins. with only anesthetic part of right hand in warm water.
	22.8	...	31.41	10 20.29 20.29 4.82 Next 10 minutes.
	22.8	...	31.52	4 16.83 16.83 4.00 First 4 mins. immersion of right wrist also in warm water.	
	22.8	...	31.63	8 26.33 26.33 6.25 Next 8 minutes.
	22.7	...	31.78	8 18.42 18.42 4.37 First 8 mins. immersion of anesthetic part only of right hand in cold water.	

TABLE V.—Continued.
SUMMARY OF RESULTS ON R. E.

Date.	Temperature C. of			Vol. of hand in c.c.	Heat given off in small calories.	Blood flow grns. per min.	Flow per 100 c.c. of hand per min.	Notes.
	Right.	Left.	Ar. Bld.					
May 8	22.7 22.8	31.83 31.85	282 480	5 9	12.24 11.13
May 18	24.8 24.8 24.6	30.98 31.02 31.11	36.55	391	409 1,158	1,317 630 383	18 10 6	12.83 12.66 13.04
	24.6 24.9	31.19 31.35	524 1,146	6 13	14.57 18.83
	24.8	31.52	650	8	17.94
	24.7	31.61	616	12	11.54
	24.9	31.67	410	5	18.67
	24.9	31.73	308	6	11.83
	24.9	31.79	598	8	17.44

TABLE VI.
SUMMARY OF BLOOD FLOW OBSERVATIONS ON O. C. W. (See p. 162)

Date.	Temperature C. of calorimeter.			Vol. of hands, c.c.			Heat given off (small cal.s.).			Flow in hands per min.			Flow per 100 c.c. per min.			Notes.
	Room.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	Right.	Left.	
Oct. 15	22.6	31.32	31.35	36.65	447	436	2,537	2,273	16	33.05	29.78	7.39	6.83	Before vasoconstrictor reflex tests. Anesthetic phabs. in cold water (first 2 mins.). Anesthetic phabs. in cold water (next 7 mins.). Anesthetic phabs. in warm water (first 3 mins.). Anesthetic phabs. in warm water (next 5 mins.). Whole left hand in warm water (first 4 mins.). Whole left hand in warm water (next 4 mins.). Whole left hand in cold water.		
	22.8	31.61	31.72	31.77	447	436	1,555	1,053	2	17.08	7.39	3.82	3.82	...		
	22.9	31.72	31.87	31.87	447	436	1,053	431	7	33.90	33.39	7.58	7.24	...		
	23.0	31.87	32.04	32.04	447	436	1,157	5	3	55.77	55.77	12.47	12.47	...		
	23.1	32.23	32.39	32.39	447	436	638	915	4	40.06	59.66	8.96	13.34	...		
	23.2	32.39	32.55	32.55	447	436	956	956	8	32.38	32.38	7.24	7.24	...		
	23.3	31.17	31.17	36.55	431	407	2,219	2,018	10	45.82	41.67	10.63	10.23	...		
	23.3	31.46	31.64	31.64	447	436	206	1,394	2	22.48	39.43	5.21	9.15	...		
	23.3	31.64	31.87	31.87	447	436	567	567	8	33.65	33.65	7.80	7.80	...		
	23.3	31.87	32.06	32.06	447	436	1,153	464	7	40.76	39.96	9.45	9.45	...		
	23.3	32.25	32.50	32.50	447	436	1,669	1,032	3	57.23	34.06	9.27	13.27	...		
	23.3	32.50	32.81	32.81	447	436	1,032	1,032	9	40.49	40.49	7.90	7.90	...		
	23.25	33.01	33.01	33.01	447	436	1,032	1,032	8	40.49	40.49	9.39	9.39	...		
	23.25	33.01	33.01	33.01	447	436	1,032	1,032	8	40.49	40.49	9.39	9.39	...		

TABLE VI.—*Continued.*
SUMMARY OF BLOOD FLOW OBSERVATIONS ON O. C. W.

Date.	Temperature C. of calorimeters.			Vol. of hands, c.c.	Heat given off (small ears).	Flow in hands per min., per 100 c.c. per min.	Notes.
	Right.	Left.	Both.				
Dec. 21	22.9	30.82	36.50	431	2,012	43.73	10.14
	22.9	31.10	36.50	431	242	24.89	5.77
	22.9	31.33	36.50	431	1,684	45.26	10.50
	22.6	31.58	36.50	431	416	31.31	7.28
	22.5	31.79	36.50	431	1,448	48.79	11.32
	22.7	31.99	36.50	431	263	32.39	7.51
	22.95	32.23	36.50	431	1,782	46.37	10.75
	23.25	32.54	36.50	431	1,110	34.60	8.02
	23.35	32.70	36.50	431	440	43.27	10.04
	23.25	32.98	36.50	431	1,160	61.02	14.15

hand flows was established which could be connected with the unilateral character of the pulmonary lesion, a fact which at first sight seemed very puzzling, came out, namely, that the hand flow was in general large in these chronic cases with extensive fibroid change, whereas in early pulmonary tuberculosis it was apt to be small. This difference as well as the unusual stability of the large hand flow in some of the chronic cases against changes of external temperature suggested that the anatomical changes in the vascular path through the lungs are a factor. If the total vascular path in the lungs is narrowed the output of the heart per minute can still remain normal if the average linear velocity of the blood in the still functioning parts of the pulmonary circuit is correspondingly increased. This would not require the return of a greater volume of blood per unit of time to the right side of the heart and therefore would not entail a diminution in the quantity of blood circulating in the peripheral parts (see Section on the *Anæmias*, p. 113). Nor would it necessarily entail any increase in the rate of the heart. If then the heart rate is substantially increased, as in all these cases, the normal flow through the diminished lung area may be maintained while an amount of blood even greater than the normal passes through the hands. The better filling of the peripheral paths might conceivably even act as a safety-valve against overfilling of the diminished and now unaccommodating pulmonary path.

In early tuberculosis, on the other hand, the vascular capacity of the lungs is not diminished. On the contrary, it is to be supposed that more blood than normal will be supplied to the infected area to combat the infection, and that this increase in the amount of blood going to the lungs may be obtained by vasoconstriction in parts like the hands. This suggestion is put forward with diffidence and in an entirely provisional way in the attempt to harmonize the results obtained on the two groups of cases, and further observations may show its futility.

A large number of cases of unilateral pleural effusion were examined from the same standpoint. In the great majority of these a deficiency in the hand flow on the side of the effusion

was found. But that this is not associated with the more mechanical effect of the fluid in the sac seems to be indicated by the fact that on removal of the liquid the difference is not, as a rule, abolished. There is some reason for thinking that it is the anatomical change in the pleura itself, the extension, for instance, of the tubercular process to the pleura from the lung, and not the presence of fluid as such in the sac, which is the factor really associated with the change in the hand flow. It must be remembered that the hand flow measurements are made with the patient in the sitting posture, so that fluid in the pleural sac will not in general occupy the part of the sac in relation with the subclavian vessels. For some time after the withdrawal of the fluid the hand flow is apt to be decidedly diminished on both sides, possibly because the expansion of the previously compressed lung entails the provision of a large total volume of blood for the pulmonary circuit.⁵

In pulmonary emphysema the hand flow also tends to be large. The same explanation might be offered as in the cases of advanced tuberculosis.

SECTION X. MISCELLANEOUS CASES

A considerable number of cases not coming under any of the above headings were studied. The only one which will be mentioned here, on account of the exigencies of space, is a case of Graves's disease. The flow in the hands was exceptionally large, a fact quite in agreement with the flushed surface, the subjective feeling of warmth and the rapid and strong pulse. Immersion of the left hand in cold water (which was very disagreeable to the patient) caused a reduction of the flow in the right hand from 14.18 grammes to 7.82 grammes per 100 c.c. per minute, and the reduction persisted during the period of immersion (5½ minutes).

⁵ The work on the cases with fluid in the pleural cavities was done in collaboration with Dr. Bucher of the Cleveland City Hospital resident staff.

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TABLE V.
SUMMARY OF RESULTS ON R. E. (See p. 142.)

Date.	Temperature C. of			Heat given off in small calories.	Blood flow gms. per min.	Flow per 100 c.c. of hand per min.			Notes.	
	Right.	Left.	Arter. Bld.			Right.	Left.	Right.		
April 26	24.0	30.82	36.6	379	951	1,469	15	12.19	3.21	4.56
	...	30.85	30.78	459	595	6	14.78	3.90
	24.0	...	30.88	444	6	...	4.71
	23.6	...	31.04	1,161	8	14.37	3.56
	...	31.18	287	3	...	29.00	7.19
	...	31.22	636	12	...	4.86
May 2	25.4	31.10	31.19	36.6	361	385	541	578	10	10.93
	25.4	31.14	237	...	5.64	...
	24.9	31.28	1,150	...	8	30.02
	25.0	31.44	271	...	2	29.18
	...	31.55	423	...	6	15.51
May 8	22.9	31.04	31.06	36.95	403	421	1,213	1,407	12	19.00
	22.9	...	31.27	22.12
	22.8	...	31.41	4.71
	22.8	...	31.52
	22.8	...	31.63
	22.7	...	31.78

TABLE V.—*Continued.*
SUMMARY OF RESULTS ON R. E.

TABLE VI.
SUMMARY OF BLOOD FLOW OBSERVATIONS ON O. C. W. (See p. 162)

Date.	Temperature C. of calorimeter.				Vol. of hands, c.c.	Heat given off (small cals.).	In mins.	Flow in hands per min.			Flow per 100 c.c. per min.	Notes.
	Room.	Right.	Left.	Arter. Blood.				Right.	Left.	Right.		
Oct. 15	22.6	31.32	31.35	36.65	447	436	2.537	16	33.05	29.78	7.39	6.83
	22.8	31.61	1.55	2	17.08	...	3.82	...
	22.9	31.72	1.053	...	7	33.90	...	7.58
	23.0	31.87	431	...	3	33.39	...	7.24
	23.1	32.04	1.157	...	5	55.77	...	12.47
	23.2	32.23	638	...	4	40.09	...	8.96
	23.2	32.39	915	...	4	59.66	...	13.34
	23.3	32.55	956	...	8	32.38	...	7.24
Dec. 19	23.3	31.17	31.17	36.55	431	407	2.219	10	45.82	41.67	10.63	10.23
	23.3	31.46	2.206	2	22.48	...	5.21	...
	23.3	31.64	1.394	...	8	39.43	...	9.15
	23.3	31.87	567	...	4	33.65	...	7.80
	23.35	32.06	1.153	...	7	40.76	...	9.45
	23.3	32.25	464	...	3	39.96	...	9.27
	23.3	32.50	1.669	...	8	57.23	...	13.27
	23.2	32.81	1.032	...	9	34.06	...	7.90
	23.25	33.01	1.032	...	8	40.49	...	9.39

Whole left hand dried and wrapped up.

TABLE VI.—*Continued.*
SUMMARY OF BLOOD FLOW OBSERVATIONS ON O. C. W.

Date.	Temperature C. of calorimeters.			Vol. of hands, c.c.	Heat given off (small ears).	Flow in hands per min.	Flow per 100 c.c. per min.	Notes.
	Right.	Left.	Right.					
Dec. 21	22.9	30.82	31.10	36.50	431	2,012	10.14	Before vasomotor tests.
	22.9	31.10	31.33	36.50	431	242	5.77	Anesthetic phal., in cold water (first 2 mins.).
	22.9	31.33	31.55	36.50	431	1,684	10.50	Anesthetic phal., in cold water (next 8 mins.).
	22.6	31.55	31.79	36.50	431	416	7.28	Anesthetic phal., in warm water (first 3 mins.).
	22.5	31.79	31.99	36.50	431	1,448	11.32	Anesthetic phal., in warm water (next 7 mins.).
	22.7	31.99	32.23	36.50	431	263	7.51	7 phals, left hand in warm water (1st 2 mins.).
	22.95	32.23	32.54	36.50	431	1,782	10.75	7 phals, left hand in warm water (next 10 mins.).
	23.25	32.54	32.70	36.50	431	1,110	8.02	7 phals of left hand in cold water.
	23.35	32.70	32.98	36.50	431	440	10.04	Whole left hand in cold water.
	23.25	32.98	33.23	36.50	431	1,160	14.15	Whole left hand in warm water (next 6 mins.).

persist for years unless fibrin forms over the surface and stimulates the growth of fibroblasts to bridge over the defect. Occasionally two or more layers of fibrin form at different times over the same site. The connective tissue replacing them can be recognized like the layers marking the annual growth of a tree.

So far as thrombi within the vessels are concerned, the lining endothelial cells quickly cover over the surface of any fibrin within the lumen and dip down into any fissures present in it, but, so far as my observations go, never form capillaries which penetrate the fibrin. Such vessels arise only from the capillaries entering the vessels from without.

Only the endothelial cells and the fibroblasts in a blood-vessel regenerate. Apparently the smooth muscle cells never do. Under certain conditions, as in syphilis, continued injury and regeneration of fibroblasts often lead to marked increase of the connective tissue. The increase of connective tissue in the walls of blood-vessels due to proliferation of the fibroblasts as the result of continued or chronic injury, and therefore to be classed as regenerative, and that due to direct stimulation by fibrin is of the greatest importance to these structures, because it may greatly impair or completely destroy their function of carrying nutrition to the tissues.

Infectious lesions due to a septicæmia tend to be distributed more or less uniformly throughout the body. They may be few in number or very numerous. Acute generalized miliary tuberculosis furnishes a very good example of the distribution and varying number of the lesions which may be produced, because they all start as lesions of the blood-vessels, chiefly the capillaries, although we do not ordinarily think of them in that way.

Lesions of the vessels start wherever the micro-organisms find lodgement and as a rule enlarge as long as the infectious agent thrives and the patient lives. Some organisms develop and produce lesions in certain organs and tissues more readily than in others; thus, the staphylococcus aureus in the kidney and heart and the tubercle bacillus in the lung and liver. Some organisms infect only capillaries and sometimes only



Fig. 1.



Fig. 2.

FIG. 1.—Organized thrombus in an artery in the kidney, showing replacement of the fibrin by fibroblasts.

FIG. 2.—Organizing thrombus of aorta. The fibrin is stained black. The light spaces in it are fibroblasts which are gradually replacing it.

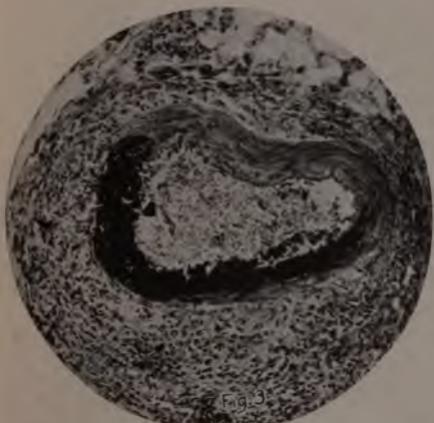


Fig. 3.

FIG. 3.—Acute infectious lesion in wall of artery in heart from a girl eight years old, dying from acute purulent arthritis, due to the streptococcus pyogenes and secondary to scarlet fever and diphtheria.



Fig. 4.

FIG. 4.—Acute infectious lesion in wall of artery of heart from same case as Fig. 3. The wall is yielding, forming an infectious aneurism.

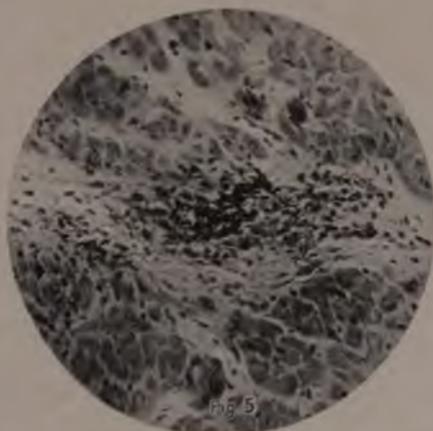


Fig. 5.

FIG. 5.—Lesion in heart from a man nineteen years old who died from acute articular rheumatism. The lesion shows fibrin and endothelial leucocytes.



Fig. 6.

FIG. 6.—A later lesion from the same case as Fig. 5, showing replacement of muscle fibres in part of wall of artery by scar tissue and a focal lesion in the neighborhood, consisting of endothelial leucocytes and fibroblasts with a few lymphocytes at the periphery.

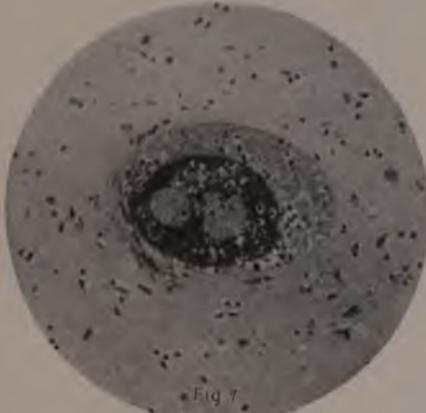


Fig. 7.

FIG. 7.—Cross section of two branches of an artery in the cerebrum. The wall is infiltrated with numerous anthrax bacilli which are extending into the surrounding tissue. The vessel is surrounded by a zone of hemorrhage.

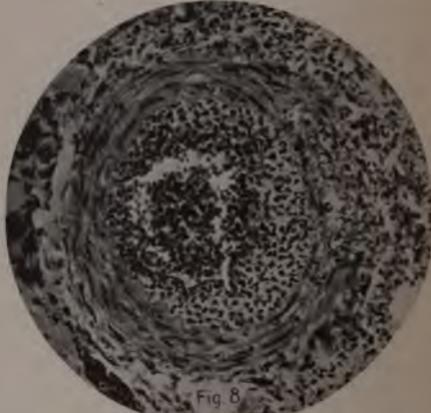


Fig. 8.

FIG. 8.—From a case of glanders. Cross section of artery in lung, showing numerous polymorphonuclear leucocytes collected beneath the lining endothelium and at one point where the muscle cells seem to be destroyed, extending through into the surrounding tissue.

those in certain organs, while others, like the leprosy bacillus, may start in vessels of any character.

The streptococcus perhaps more than any other of the pus-producing organisms causes, when present in the circulation, a variety of lesions, which may vary even in the same patient from simple necrosis followed by repair, because the cocci all die, to complete destruction of the wall and abscess formation. Four cases due to organisms which were not very virulent, and which readily died in the lesions they caused, will illustrate the character and termination of the infectious lesions of the milder type.

In the first, a girl eight years old, death occurred from acute purulent arthritis secondary to scarlet fever and diphtheria and due to the streptococcus pyogenes. Multiple acute infectious lesions of the blood-vessels were found in the heart (Fig. 3), kidneys and liver. They all showed practically the same kind of histological change, necrosis of a part of the vessel wall, with considerable fibrin formation and the accumulation of numerous polymorphonuclear and endothelial leucocytes and some lymphocytes in the perivascular tissue adjoining the site of the injury. But little fibrin was deposited as thrombus within the vessels. It was either in the wall or on the outside. In one of the arteries in the heart the injured wall had yielded to the blood-pressure, forming an aneurism of infectious origin (Fig. 4).

The second patient was a male, nineteen years of age, who died from typical acute articular rheumatism of two weeks' duration, complicated at the end with lobar pneumonia. There was a slight mitral endocarditis in addition. Numerous lesions were found in the heart, occurring in the walls of the arteries and extending into the surrounding connective tissue. They were milder in type than in the preceding case and evidently in the stage of repair. Some showed considerable fibrin and numerous endothelial leucocytes (Fig. 5). Strands of collagen fibrils left by necrotic fibroblasts were surrounded by them in places. Alongside some of the vessels focal cellular areas of connective tissue, due to proliferation of the fibroblasts, were

present, surrounded and infiltrated by a few lymphocytes (Fig. 6). These are the lesions considered characteristic of acute articular rheumatism. They do not differ from those already described except in intensity.

In a third case, recently reported by Palfrey and Ayer, the patient, a woman aged thirty-three years, died from chronic infectious endocarditis of the mitral valve, due to a streptococcus corresponding in type to that described by Poynton and Payne. The heart showed a number of infectious lesions in the walls of the blood-vessels and in the surrounding connective tissue. Some were acute and others healing. The important point is that all stages in the development of lesions corresponding to those described in the first two cases were present.

In the liver and kidneys and in muscle tissue from a case of periarteritis nodosa, reported by Longcope, some of the lesions are acute and exactly like those described in case one. Others are in all stages of repair. The lesion is peculiar only in one respect: Evidently much fibrin was formed within and outside of the vessels and has led to marked proliferation of fibroblasts, so that the walls of some of the vessels are greatly thickened. Many are also completely occluded by thrombus formation.

These four cases illustrate very clearly the different types of infectious lesions produced in blood-vessels by organisms, usually varieties of the streptococcus, which are not too virulent and which die quickly after causing an injury, thus giving opportunity for repair. It seems fair to conclude that the lesion often found in the heart in acute articular rheumatism is characteristic, not of that disease, but only of an acute infectious process which started in the walls of blood-vessels and extended to the adjoining connective tissue. Similar lesions may occur in the heart in other infections which have not presented the symptoms characteristic of acute articular rheumatism.

Certain other micro-organisms which more or less frequently infect blood-vessels require especial consideration, because the lesions which they cause differ in some respects from those which I have already described. They are the bacilli of

glanders, tuberculosis and leprosy, and the *treponema pallidum*. In order to understand fully the lesions which they produce it will be necessary to describe briefly the nature of the inflammatory reaction which each of these infectious agents brings about in the human body.

The reaction to the glanders bacillus differs least from that of the ordinary so-called pus-cocci. The micro-organism usually multiplies abundantly in the lesions and gives rise to a strong toxin which gradually causes necrosis of all the surrounding cells. The inflammatory reaction in the tissues consists of an exudation of serum and of numerous polymorphonuclear and endothelial leucocytes. Usually but little fibrin is formed. The result is abscess formation. The distinguishing and apparently characteristic feature of the inflammatory reaction, which renders it possible to recognize the lesions histologically with at least a fair degree of certainty, is the presence of large cells with large lobulated or sometimes with multiple nuclei. These large cells develop from the endothelial leucocytes apparently as the result of the action of the toxin derived from the bacilli. The toxin seems to affect these leucocytes in much the same way that the diphtheria toxin sometimes affects epithelial cells, producing direct division of the nuclei and increase in the amount of cytoplasm.

The blood-vessels are often infected in glanders. When they are involved from without, the vessel wall may gradually undergo necrosis and polymorphonuclear leucocytes may collect in large numbers beneath the lining endothelium (Fig. 8). The characteristic lesions are formed, however, within the vessels, most often in veins, by the immediate presence of the bacilli. The cellular reaction of polymorphonuclear and endothelial leucocytes around them, together with the formation of more or less fibrin, lead to obstruction of the vessels and often to extension of the thrombotic process along them. Involvement of the surrounding tissue by direct extension and abscess formation is the usual termination. The interesting point is that the large multilobulated cells already described are usually present in these cellular thrombi.

The inflammatory reaction to the tubercle bacillus is best studied in cases of acute miliary tuberculosis. As a rule all stages in the development of the lesions can be found. The bacilli escaping into the blood stream from some primary focus, whether they are free or within polymorphonuclear leucocytes, are quickly taken up by the endothelial cells lining the blood-vessels, usually the capillaries, less often the larger vessels, the veins and the arteries. The liver furnishes perhaps the best material for study but the process can be followed in the lung and other organs and occasionally even in the capillaries of the glomeruli of the kidney.

The tubercle bacilli do not cause, certainly at first, any apparent injury to the endothelial cells. They often multiply within them although never to the extent that leprosy bacilli do, except in avian tuberculosis. The toxin emanating from them attracts endothelial leucocytes which collect in the sinusoids and surround the cell originally infected, forming the early miliary tubercle, which at this stage cannot be told histologically from that developing around a dead and dissolving typhoid bacillus except by the presence of the tubercle bacilli. The tubercle bacillus may multiply rapidly and gradually invade, apparently by direct growth, these endothelial leucocytes in its immediate neighborhood, or more often multiply slowly so that each lesion contains only a few or even only a single organism. The miliary tubercle represents the limit to which the attractive influence of the toxin extends out from the bacilli in the lesion. The function of the endothelial leucocytes is reparative. They are the cells best fitted to counteract chemically the toxin derived from the tubercle bacillus.

Sometimes polymorphonuclear leucocytes are attracted in small or large numbers around the tubercle bacillus, especially with certain strains which multiply rapidly.

The further progress in the development of the miliary tubercle is as follows: The endothelial leucocytes attracted around the cell originally infected gradually occlude the sinusoids and cut off the circulation, thus diminishing the supply

of nutrition to the cells in the center of the lesion. The liver cells undergo necrosis first and then the more resistant fibroblasts and endothelial cells. The products from these necrotic cells also attract leucocytes to dissolve and remove them and to counteract the injurious substances arising from them just as happens, for example, around a bland infarct. As soon as necrosis of fibroblasts has occurred proliferation of the surrounding fibroblasts begins. Apparently they are the only cells which regenerate. They soon form a zone around the tubercle, provided the latter is not developing too rapidly, under which circumstances no regeneration may occur. The periphery of the tubercle is usually infiltrated with a certain number of lymphocytes and occasionally with a few eosinophiles. Usually some of the endothelial leucocytes fuse to form one or more foreign body giant cells, apparently around the fatty substances derived from the tubercle bacilli. Similar giant cells will develop in experimental lesions produced by injecting the fat or wax extracted chemically from cultures of the bacillus.

Fibrin often forms in considerable quantity in miliary tubercles after necrosis has occurred and may play some part in the repair of the lesion by stimulating the fibroblasts to proliferate.

It is evident from this statement that in the early miliary tubercle the so-called epithelioid cells are endothelial leucocytes. In the older tubercles many of them may be fibroblasts and if the bacilli die out the endothelial leucocytes disappear and continued regeneration of the fibroblasts results in the so-called fibrous tubercle which finally terminates in a small mass of hyaline fibrous connective tissue.

The necrosis in tuberculosis is certainly due in large part, if not entirely, to endothelial leucocytes attracted by the toxin infiltrating the blood and lymph vessels and lymph spaces and cutting off nutrition. As a rule the tissue cells disappear first, the leucocytes last. On this account the landmarks in necrotic tissue of tuberculous origin are usually more or less completely obliterated.

The lymphocytes in and around tuberculous lesions are, per-

haps, attracted more by products derived from the necrotic cells than from the tubercle bacillus.

The miliary tubercle goes on developing peripherally in more or less perfect, spherical form practically only in the brain. The reason of this is that in most organs and tissues the tubercle bacilli quickly gain entrance to blood or lymph spaces or epithelial-lined cavities and spread rapidly through them.

It is the anatomical structure of organs and tissues which is chiefly responsible for the great variety of gross appearances presented by the lesions due to the tubercle bacillus. Compare, for example, the caseous mass of a solitary tubercle of the brain with the fibrinopurulent type of meningitis which may be produced as soon as the same organism reaches the surface of the brain and gains access to the abundant nutrition furnished in the wide lymph spaces of the meninges.

The reaction in these larger cavities of various kinds is essentially the same as in the miliary tubercle. The endothelial leucocyte is the most important cell in counteracting the injurious influence of the tubercle bacillus and its toxin, although when the organisms multiply rapidly the polymorphonuclear leucocytes may play an active part. Serum often collects in considerable amount and much fibrin may be formed from it, as for instance in the alveoli of the lung. This fibrin often leads to organization within the alveoli just as it does in the pleural and pericardial cavities. Much of the fibrous tissue in old tuberculous lesions of the lungs is evidently of this origin. Naturally some of it is later destroyed again if tubercle bacilli remain behind after organization because they start new lesions. Lymphocytes often mingle in the exudation in considerable numbers.

With this understanding of the reaction of the body to the injurious effect produced by the tubercle bacillus, the tuberculous lesions of blood-vessels may be presented in a few words. Lesions in the capillaries are very common and have already been covered in the description of the miliary tubercle. In the terminal veins of the spleen the endothelial leucocytes sometimes collect in such large numbers as to distend and occlude

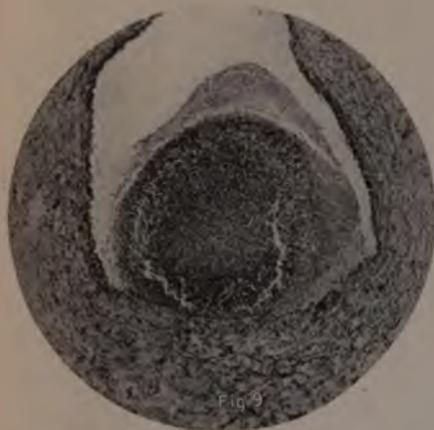


Fig. 9



Fig. 10

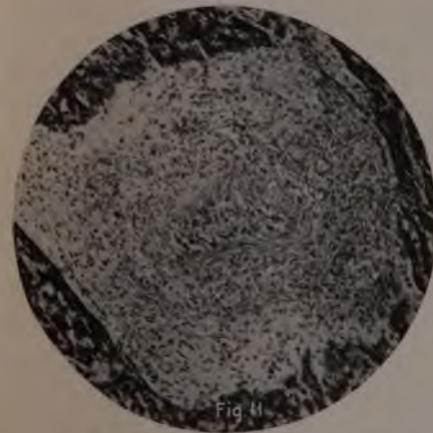


Fig. 11

FIG. 11.—Cross section of artery in the heart from a case of congenital syphilis, showing marked inflammatory infiltration around the vessel.

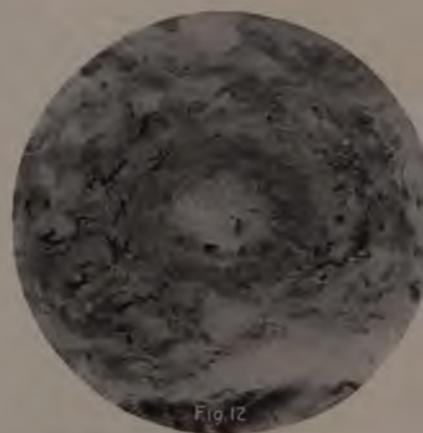


Fig. 12

FIG. 12.—From the same case of congenital syphilis of the heart as Fig. 11, stained by Levadit method to show the numerous spirochaetes present.

them. They form what may be called endothelial cell thrombi.

The larger blood-vessels, both veins and arteries, are most often infected from without by direct extension of tuberculous lesions surrounding them. Such infections of the vessels can frequently be found in the meninges and in the lungs. The bacilli may invade the intima and give rise to miliary tubercles lying beneath the endothelial lining, or more commonly to the formation of thrombi consisting of fibrin or of endothelial leucocytes or of a varying combination of these two elements. In the fibrinous thrombus the tubercle bacilli may develop in great numbers and later by softening and rupture of the thrombus be discharged into the circulation (Figs. 9 and 10). Evidently fibrin under certain conditions is an excellent culture medium for this organism. Infection of the larger blood-vessels from the intimal side is rare but possible; miliary tubercles have been found even on the inner surface of the aorta.

Tuberculous lesions of the arteries and aorta have, in rare instances, caused weakening of the wall and aneurismal formation.

The tuberculous lesions of blood-vessels may be summed up in a few words. They are very common in capillaries and lead to complete occlusion of them. They occur fairly frequently in the small veins and arteries especially in certain parts of the body, such as the lungs for instance, and are dangerous because the tubercle bacilli may multiply in great numbers and by escaping into the circulation give rise to acute generalized miliary tuberculosis. They rarely lead to the formation of an aneurism in arteries or the aorta from which again large numbers of bacilli may be discharged into the blood.

The leprosy bacillus is a very mild infectious agent. It does not cause much more of an inflammatory reaction than so much inhaled carbon; that is, it acts almost mechanically, giving little or no evidence of the production of a toxin to destroy either itself or the cells in which it lives. It has, however, the deadly gift of multiplying almost indefinitely so long as the supply of nutrition is abundant.

The leprosy bacilli occur chiefly in endothelial leucocytes

which represent the inflammatory reaction to the organisms. They also invade some of the fixed tissue cells. Thus they occasionally grow into the epithelial cells of the epidermis and of the hair follicles, gradually spreading from one cell to another. They occur more frequently in the epithelium lining the coil glands of the skin and occasionally free in masses within the lumina. From these sources by desquamation and perspiration they may be set free from the body. In none of these situations do they cause any inflammatory reaction. Occasionally they invade fibroblasts and fat cells, and a few apparently unquestionably occur free between the cells and fibrils of the tissues. The chief damage produced is done by the endothelial leucocytes which often contain the bacilli in large numbers, dozens to hundreds. The leucocytes crowd the tissues everywhere and utilize much of the nutrition brought to the part. They invade the nerves, carrying the bacilli with them and gradually lead to atrophy and disappearance of the nerve fibres and consequent anaesthesia.

It is difficult to determine how much injury and destruction of the fixed cells occur in leprosy and how it is produced, whether by the direct action of the bacilli or as the result of pressure from the presence of so many endothelial leucocytes, because the cell changes are so exceedingly slow and slight. Nerve fibres disappear and fat cells undergo necrosis leading to the formation of giant cells around the fat set free. The connective tissue gradually increases in amount as the result apparently of regeneration following injury of some sort or other.

The changes in the blood-vessels are not prominent. Bacilli are very often present in small to large numbers in the lining endothelium of capillaries, veins and arteries. They attract no leucocytes as tubercle bacilli would do and produce no visible effect of any sort. They do not even seem to invade the adjoining tissue. Another type of lesion is due to the presence of endothelial leucocytes filled with bacilli in the vessel wall which may in consequence be considerably thickened. The bacilli sometimes invade the fibroblasts near them. Such vessels may in time show much thickening of their walls with nar-

rowing of their lumina and disappearance of the smooth muscle cells. The atrophy of leprosy nodules and scar tissue formation may perhaps be dependent in part at least on sclerosis of blood-vessels.

The lesions of syphilis are the most difficult of all the infectious processes to obtain a clear and positive understanding of, for two reasons. Material for histological study is hard to obtain and it is practically impossible at present to show the infectious agent, the *treponema pallidum*, in the same preparations with the inflammatory reaction. The organism must be demonstrated in a parallel series of sections in which the cell changes often show but poorly. Moreover the Levaditi method often fails to stain the spirochaetes, especially in perfectly fresh tissue, and antisyphilitic treatment may have caused the disappearance of the organisms before the tissue used for study was obtained. I can only present the views I have arrived at as a result of the study of such material as has been available.

Evidently the *treponema pallidum* is an organism of slight virulence. It produces a very mild toxin which is locally diffusible and is absorbed along the lymph spaces and vessels. The primary direct injury caused by it must be exceedingly slight. The organism has to be present, certainly as a rule, in large numbers to produce any visible injury. The lesions it causes develop so slowly that regeneration is usually a marked feature and may be more prominent than the inflammatory exudation. On the other hand injury of secondary origin due to obstruction of blood-vessels is usually a marked feature of the later manifestation of the disease.

The *treponema pallidum* may invade any tissue in any number. It occurs often in the epidermis but is found especially in connective tissue wherever present, in organs and tissues in general and in the walls of blood-vessels. In connective tissue it lies in the minute spaces between the cells and especially between the collagen fibrils where great numbers of the organisms often accumulate.

The inflammatory reaction on the part of the body is not

easy to determine with certainty. The organisms may be fairly numerous in the epidermis with no reaction around them. Then polymorphonuclear or endothelial leucocytes or both make their appearance between the epithelial cells. As they increase in number the treponemata are likely to disappear although sometimes they increase in number. Evidently the epithelium is slowly injured in some way or other because ulceration often occurs.

In connective tissue in like manner the organisms are often present in enormous numbers with little or no inflammatory reaction around them. As a rule, however, the tissue is infiltrated with varying numbers of endothelial leucocytes and lymphocytes; many of the latter occur in the form known as plasma cells. Sometimes polymorphonuclear leucocytes are also added to the exudation, although they are rarely numerous.

In the primary lesion or chancre the injury and reaction, except for surface ulceration, do not, under ordinary conditions, go beyond this stage. The inflammatory infiltration with leucocytes and lymphocytes does not represent, however, all that has occurred in the lesion. There has also been a considerable proliferation of fibroblasts, regenerative in character, evidently the result of injury produced slowly and gradually by the mild toxin derived from the spirochaetes. Some of the fibroblasts have undergone necrosis and others have proliferated in order to replace them. The regeneration as usual has been in excess of the actual number of cells destroyed so that an increased amount of fibrous tissue has resulted.

After a certain fairly definite period of time the primary lesion undergoes repair, apparently as the result of acquired local immunity. It does not tend to spread indefinitely as a tuberculous lesion, for example, would do. The treponemata die probably as the result of the production of effective antibodies either by the leucocytes in the circulation or more probably by those attracted into the lesion. The leucocytes gradually disappear from the lesion, the ulceration heals, and the connective tissue contracts, leaving in the end a scar.

In the later lesions of syphilis the same kind of cell reaction



Fig. 13.



Fig. 14.

FIG. 13.—From a case of acquired syphilis in which the figure shows a cross section of an liver. The lumen is nearly occluded by necrotic tissue in which is one distinct nodule.

FIG. 14.—Syphilitic endaortitis due to acquired syphilis in an adult; elastic tissue stain. The section shows marked thickening of the intima with necrosis extending deeply into the underlying muscle coat.

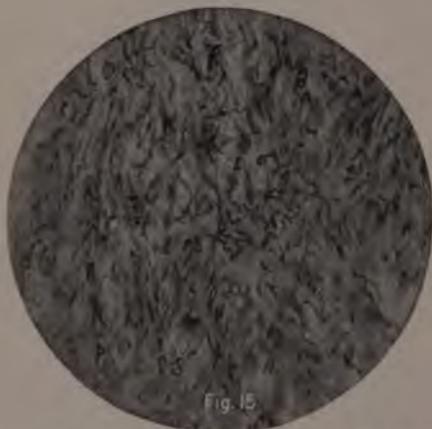


Fig. 15.

FIG. 15.—From the same case as Fig. 14 to show the numerous treponemata pallida present. (From a case which has been reported by Dr. J. H. Wright of the Massachusetts General Hospital.)

is repeated, but it is often complicated by evident and frequently extensive necrosis forming the so-called *gummata*. Much if not all of this necrosis follows as the result of occlusion of blood-vessels and cutting off of the blood supply. In syphilis of the liver, for instance, it is often possible to find both types of lesions present; extensive areas of necrosis and a diffuse inflammatory process showing more or less, occasionally marked, infiltration with polymorphonuclear or endothelial leucocytes. In addition there is always increase in the amount of connective tissue of regenerative origin. Apparently there is no essential difference in the actual injury and reaction caused by the *treponema* in the primary and later lesions which it produces. On the other hand it is exceedingly difficult to determine whether the leucocytes are attracted by the organism, its toxin, or the products of the destroyed cells.

The actual tissue lesion in congenital syphilis differs from that in the acquired disease apparently only in degree. The *treponemata* are usually much more widely distributed, and are present in relatively much larger numbers; but they produce as a rule less inflammatory reaction and rarely lead to obstruction of blood-vessels and consequent necrosis. On the other hand the proliferation of fibrous tissue is usually abundant and ordinarily the most marked feature of the process.

Syphilitic lesions of the blood-vessels are of frequent occurrence and of a great importance. The *treponemata* are present more often in the adventitia than in the intima but both locations are often infected at the same time. The media may thus be involved from either or from both sides. The intima on one side or all around may rapidly thicken up and cause narrowing or complete occlusion of the lumen. The thickening is due to an infiltration of endothelial leucocytes often combined with lymphocytes and occasionally with polymorphonuclear leucocytes. In addition the fibroblasts proliferate (Fig. 13). The cell changes correspond with those produced elsewhere by the *treponemata*. As soon as the blood supply is cut off completely, necrosis occurs and more or less fibrin is formed.

In the adventitia much the same reaction takes place (Figs.

11 and 12). As soon as necrosis occurs, probably as the result of occlusion of blood-vessels, numerous endothelial or polymorphonuclear leucocytes or both are attracted by the products of the disintegrating cells. Occasionally some of the endothelial leucocytes fuse around substances hard to dissolve, such as elastic fibrils, masses of fibrin, or fat and its products, to form foreign body giant cells.

Syphilitic lesions of the aorta have always attracted much attention and excited a great deal of discussion, but the demonstration of treponemata in them, often in large numbers, has decided in favor of their actual occurrence. The organisms may invade the aorta directly from without or through the nutrient vessels of the wall, but certainly in many instances they infect the vessel from the intimal side. The lesions (Figs. 14 and 15) often extend deeply into the underlying tissue, causing necrosis and frequently softening with subsequent repair and scar formation or yielding of the wall in the form of aneurisms. Fibrin often forms in abundance and later may undergo more or less extensive organization.

As already stated necrosis occurs in tuberculous lesions usually owing to complete infiltration of the tissues with endothelial leucocytes which block all the smaller vessels, causing necrosis and disappearance of the tissue cells before they themselves undergo necrosis. Consequently all the landmarks have been obliterated. In syphilis, on the contrary, the necrosis results largely or entirely from the obliteration of blood-vessels and the tissue which undergoes necrosis may show only moderate inflammatory infiltration and proliferation of fibroblasts or none at all.

NOTE.—The lecture was illustrated by fifty-nine lantern slides made from photomicrographs, of which fifteen are reproduced here.

ANTITYPHOID VACCINATION*

MAJOR FREDERICK F. RUSSELL
U. S. Army =

MR. CHAIRMAN, ladies and gentlemen: I thank you for the honor you have done the Medical Corps of the Army in inviting me to give one of the lectures before this Society.

The subject for the evening was selected by your committee and I shall, therefore, endeavor to do justice to it and to put before you, as briefly and concisely as possible, the main points of interest offered by antityphoid vaccination, and in so doing to convince you that it has a great and promising field of usefulness in the United States, both in civil life and in the Army.

We shall consider in turn the history of the subject, the methods of preparing the vaccine, its standardization and dosage, the indications for its use, the results already obtained and its probable value in the future.

The basis upon which the practice of antityphoid vaccination has been built is, of course, the observation that one attack of typhoid fever almost invariably gives permanent immunity against subsequent attacks. Of 2,000 cases in the Hamburg General Hospital, only fourteen persons were affected twice, and but one, three times (Dreschfeld). In 500 of Osler's cases in which special inquiry was made as to previous attack, it was found to have occurred in eleven, or 2.2 per cent. It is interesting to note that although the immunity usually lasts during life, the immune bodies, nevertheless, disappear from the blood of convalescents within a few months.

The harmlessness of inoculating killed typhoid bacilli into human beings was demonstrated in the year 1896, by Sir. A. E. Wright in England, and Pfeiffer and Kolle in Germany. The publication of Pfeiffer and Kolle's investigations¹ antedates

* Delivered January 18, 1913.

¹ Deutsche Med. Wehnschr., 1896, xxii, 735.

Wright's paper by some months. The researches of Pfeiffer and Kolle were carried out on two men and were remarkably complete and comprehensive, showing as far as the laboratory methods of that day permitted, the identity of the immunity following an attack of typhoid fever, with that produced by the inoculation of killed typhoid bacilli. Thus early was the procedure placed on a solid scientific basis.

Wright's first paper,² curiously, is entitled, "On the Association of Serious Hemorrhages with Conditions of Defective Blood Coagulability," and the inoculation of killed typhoid bacilli was apparently a mere incident in a research upon another subject. The following year, however, he reported on the blood changes in seventeen persons, following typhoid inoculation.³

It is in this paper that Wright mentions Kafkine's suggestion to him, made a year previously, that the method of vaccination with bacterial cultures, which had been so successfully used in the prophylaxis of cholera, might, *mutatis mutandis*, be applied to the prevention of typhoid fever. Wright appears to have been convinced by his series of seventeen cases, that the prevention of typhoid fever by vaccination was a possibility. He suggested at this time, 1897, its use in armies and among the personnel of hospitals. This really constitutes the beginning of the present vaccination campaign against typhoid fever. Wright continued his work with enthusiasm, and in 1898, while serving on the Plague Commission in India, vaccinated about 4,000 men of the British Indian Army with excellent results.⁴ Soon after his return to England in 1897, there occurred an extensive outbreak of typhoid fever at the Barming Asylum, Maidstone; and as he himself was unable to go, he sent, first Sir David Semple, and afterward Sir William B. Leishman, to carry out inoculations on about one hundred of the attendants. There, also, the results were highly gratifying, since no cases occurred among the inoculated.

² Lancet, Lond., Sept. 18, 1896, p. 807.

³ Wright, Sir A. E.: British Med. Jour., Jan. 30, 1897, p. 16.

⁴ Wright: Lancet, Lond., Sept. 6, 1902, 654.

Soon afterward, in 1900, came the Boer War, and anti-typhoid inoculation, having already given such a good account of itself, upon Wright's recommendation, its use was authorized by the War Office among the troops destined for South Africa.

The vaccination was voluntary, and, as a matter of fact, is still voluntary in every country except ours. Some men were inoculated before leaving England, others on the transport during the long voyage to South Africa, and in a few instances, in the field after arrival. For this purpose Wright and Leishman furnished some 400,000 doses but it is believed that only 100,000 men received one or more.

No complete statistics of antityphoid vaccination in South Africa have ever been published and they probably do not exist. We know in general that there were 57,684 cases of typhoid and 8,022 deaths among 380,605 men.⁵ This gives a morbidity rate of 151.56 per 1,000 of mean strength, and a mortality rate of 21.08 per 1,000; a result which does not differ markedly from our own rates in the Spanish American War, where no vaccination was in force. In our service a larger number of cases were diagnosed, but the death rate was, nevertheless, much less than in South Africa.

TABLE I.

	Total strength	Cases	Ratio per 1,000	Deaths	Ratio per 1,000
English Army, Boer War, 1900-3.....	380,605	57,684	151.56	8,022	21.08
American Army, Spanish War.....	107,973	20,738	192.6	1,580	14.62
Wright's statistics, Boer War.....	19,069	226	11.84	39	2.04

Wright collected statistics covering the inoculation of 19,069 soldiers.⁶ Among this number there were 226 cases of typhoid

⁵ Leishman: *Antityphoid Vaccination*, Glasgow Med. Jour., 1912, lxxvii, 408.

⁶ McCrae in Osler's *Modern Medicine*, 1909, ii, and Wright: *Lancet*, Lond., Sept. 6, 1902, 654.

fever, and 29 deaths, while among 150,231 unvaccinated soldiers there were 3,739 cases of typhoid fever, as appears in the following table:

TABLE II.
BOER WAR, ENGLISH TROOPS, WRIGHT'S STATISTICS.

	Number	Cases	Ratio per 1,000	Deaths	Ratio per 1,000
Vaccinated.....	19,069	226	11.84	39	2.04
Unvaccinated.....	150,231	3,739	24.88	?	?

At Ladysmith,⁷ the following results were obtained:

	Morbidity.	Mortality.
Vaccinated	1,705 35 cases 2.05%	8 deaths 0.47%
Unvaccinated	10,529 1,489 cases 14.14%	329 deaths 0.13%

At Modder River,⁸ there occurred 26 cases among 2,335 vaccinated, or 11.1 per cent and 257 cases among 10,981 unvaccinated, or 23.4 per cent.

Wright considers that the incidence of the disease was diminished about one-half and the mortality even more. His conclusions, however, were based upon incomplete statistics and were not accepted, at the time, by his colleagues in the service. The awful death roll remained in spite of explanations. It appeared to have been impossible during the war to keep accurate records or even to vaccinate systematically, and consequently the whole question was left in considerable confusion. This was made worse by the receipt of many unfavorable reports; some asserting that the vaccine did no good, others maintaining that it actually increased the number of cases and deaths.⁹

Before the end of the war, as a result of this unfavorable attitude, the British War Office suspended the practice of in-

⁷ Rep. Committee on Antityphoid Vaccination, Bulletin d'Acad. d. Med., Par., Jan. 24, 1911.

⁸ *Ibid.*

⁹ Crombie: *A. Lancet.*, Lond., 1902, i, 1201, and 1902, ii, 436.

oculation and appointed a commission to reinvestigate the whole question. Very fortunately this commission, under the chairmanship of Dr. C. J. Martin, of the Lister Institute, included in its membership, Sir William B. Leishman, to whom fell the experimental part of the proposed investigation. He conducted extensive experiments at Aldershot in regard to dosage and the changes in the blood serum following inoculation. More recently, additional studies have come from his laboratories at the Royal Army Medical College and the importance of this work of Leishman's can scarcely be overestimated; and although he made only a few changes in Wright's vaccine, they were important ones.

The typhoid committee in their statistical studies and experimental work at Aldershot, obtained evidences of a considerable degree of protection; and their interim report, rendered in 1904, was decidedly favorable. It introduced accurate and practical methods of obtaining reports from twenty-four regiments, totaling almost 20,000 men, and as the results have shown, the work was successful in rehabilitating an almost discredited procedure. As a result, inoculations were resumed in certain selected regiments, to which a medical officer, especially trained in typhoid diagnosis, was permanently attached. By this means, in a comparatively short time, accurate records were obtained. As many volunteers as possible were vaccinated before the regiments left England for India, and efforts to obtain additional volunteers were continued at the Indian stations, until the greater number of the men were vaccinated, many regiments having as many as 90 to 100 per cent. protected.

AMERICAN EXPERIENCE

For some years we had followed the work of Wright and Leishman with interest, and Wright's visit to this country, in 1907, added to our knowledge of his work with vaccines, although at that time Wright was more interested in vaccine therapy in general, than in typhoid prophylaxis. We, however, as military sanitarians, always with the possibility of a war confronting us, were more taken with Wright's former advocacy

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TABLE III.
STATISTICAL TABLE, SHOWING THE RESULTS OF ANTIYTHOID INOCULATION IN SIXTEEN UNITS OF THE BRITISH
ARMY, UP TO JUNE 1, 1808.

Unit	Medical Officer	Station	Total strength (actual)	Inoculated			Non-Inoculated			
				Number	Classes	Deaths	Number	Classes	Deaths	
2nd Roy. Fus.	Capt. A. B. Smallman.	Trimulgherry.	1,013	196	10	815	59	9		
17th Lancers.	Capt. E. J. Luxmore.	Meerut.	616	322	3	0	294	71	12	
Brigade, R. A.	Capt. E. G. Lithgow.	Pindi (from 'Trans-vaal').	370	60	0	310	7	0	
14th Hussars.	Lieut. C. E. Fawcett.	Bangalore.	647	386	2	0	261	4	1	
2nd Dorsets.	Lieut. E. G. Arthonisz.	Wellington.	1,107	199	1	0	908	6	0	
3d Coldstream Guards	Lieut. J. H. Graham.	Cairo.	705	569	1	0	136	13	1	
2nd Leicesters.	Lieut. H. S. Sherren.	Belgaum.	963	346	3	617	17	1	
1st Connaught Rangers.	Lieut. A. D. O'Carrol.	D a g s h a i (from Malta).	483	300	0	0	183	2	1	
3d Worcesters.	Lieut. W. H. Forsyth.	Wynberg.	900	220	0	0	680	3	0	
1st Dragoon Guards.	Lieut. G. H. Stevenson.	Umballa.	592	450	0	142	0	0	
1st Yorks.	Lieut. S. de C. O'Grady.	Cairo.	893	470	0	423	0	0	
1st Suffolks.	Lieut. J. B. G. Mulligan.	Malta.	900	400	0	500	0	0	
3d Roy. Rifles.	Lieut. R. W. D. Leslie Crete.	879	190	0	0	689	0	0	
2nd Bedfords.	Lieut. C. M. D'ew.	Gibraltar.	700	320	0	380	3	1	
Brigade, R. A.	Lieut. A. S. Littlejohn.	Pretoria.	375	247	1	128	2	0	
1st Lan. Fus.	Lieut. F. D. G. Howell.	Chakrata.	940	798	0	144	0	0	
		Totals.	12,083	5,473	21	2	6,610	187	26

of antityphoid vaccination, than with his newer, brilliant theories and discoveries.

The necessity for some means of preventing, or at least controlling, typhoid fever, in military camps, in addition to sanitary measures, was a continual spur, driving us on to investigate everything which offered any hope of success. It was therefore with great interest that we followed the results obtained by Col. Leishman,¹⁰ among troops of the Indian Army.

In 1909, Leishman published the first comprehensive report of the results of vaccination in certain selected Indian regiments. His table is reproduced on page 172, and may be summarized as follows:

Case-Incidence per 1,000.

	Inoculated.	Non- Inoculated.
(1) Among the whole of the above sixteen units..	3.8	28.3
(2) Among the "exposed" units, <i>i.e.</i> , in which cases of enteric had occurred	6.6	39.5
(3) "Exposed" units, <i>less</i> Royal Fusiliers (the unit inoculated with the "old vaccine").....	3.7	32.8

Summary.—There are only *four* cases among the above *twenty-one* which had received two doses of the new vaccine; all recovered. Three of the four had been noted as extremely mild, and the diagnosis of enteric in one of these is doubtful.

The experience of the 17th Lancers, which had been brought to our attention by Col. Leishman early in 1908, was so striking that we felt much encouraged about the possibility of having, at last, an effective prophylactic and so began to take an active interest in the vaccine. I had been stationed at the Army Medical School only a few months when the late Surgeon General Robert M. O'Reilly directed me to make preparations to try out the method on our own troops.

As the quickest and best way of beginning, orders were issued in June, 1908, for me to proceed to London, where I could learn from Col. Leishman and his assistants, at the Royal Army Medical College, their method of preparing the improved vaccine. There I was given the run of the laboratory, and every

¹⁰ Jour. Roy. Army Med. Corps, Lond., 1907, viii, 463, and 1909, xii, 166.

facility for learning their methods. They also were kind enough to furnish me with a transfer of the culture (Rawlings) used in preparing the vaccine.

Later in 1908, a trip was made to Berlin, where at the Institute for Infectious Diseases, I learned of the German experience with typhoid prophylactics. The complete report of the German investigations, published in 1905, is accessible and will be passed over quickly.¹¹

The occasion for the German investigation was the excessive prevalence of typhoid fever among the Colonial troops in Southwest Africa. All attempts to control the epidemic by the usual sanitary methods having been unsuccessful, recourse was had to vaccination. The Institute for Infectious Diseases was intrusted with the task of investigating the vaccines already proposed, the selection of some reliable method, and the preparation of the vaccine, should one be decided upon.

Comparative tests were made of vaccines prepared according to the methods of (1) Pfeiffer and Kolle, (2) Wright, (3) Neisser-Shiga, (4) Wassermann, and (5) Bassenge-Rimpau, by the staff of the Institute, consisting at the time of Professors Koch, Kirchner, Gaffky, Doenitz, Kolle and Wassermann.

Small groups of men were immunized with each vaccine and the blood serum was subsequently tested for bacteriolytic amoebocytes by Pfeiffer's test, and for agglutinins by the usual technic. Although the bacteriolsins and agglutinins did not run parallel, it was found that the Pfeiffer-Kolle vaccine gave a much greater degree of protection than any other, and it was therefore adopted. The investigators objected to Wright's vaccine because of his use of broth cultures, since it is well known that bacterial contaminations are difficult to avoid or to detect in fluid media.

The Pfeiffer and Kolle vaccine consisted of a salt solution suspension of fresh agar cultures of typhoid of such a strength that one cubic centimeter contained two normal loopfuls, or four milligrams of fresh bacterial substance. The bacteria were killed

¹¹ Veroffent. a. d. Gebeit des Militar-Sanitätswesens, Heft 28, Berlin, 1905.

by heating the flasks from one and one-half to two hours, in an incubator regulated for 60° C. After tests for sterility, 10 per cent of a 1/20 solution of phenol was added. The dose used at first was 1, 2, and 3 loopfuls of killed culture contained in 0.5, 1.0 and 1.5 c.c. of vaccine; as this dosage, however, produced severe general and local reactions, it was subsequently reduced to 0.4, 0.8, and 1 c.c. The interval between doses was 10 days and the site of inoculation was the breast at the level of the second rib.

This vaccine was used in the German Colonial Army, which consisted at that time of about 16,500 men, of whom 7,287 or less than one-half, volunteered for the inoculation. Among this number there were 1,277 cases of typhoid,¹² and a study of their distribution shows clearly the undeniable advantages of prophylactic inoculation, even though the results were not nearly so good as have since been obtained in India and in our own country. The weak point of the German vaccine lay, apparently, in the high temperature at which it was killed, and in the excessive dosage.

One may briefly and roughly summarize their results by saying that there was a reduction among the vaccinated of one-half in the number of cases; a much higher percentage of light attacks, 50 to 36, and a much lower percentage of fatal cases, 6.4 to 12.8. If we distinguish between those receiving 1, 2, and 3 doses, we find that the percentage of fatal cases was 60, 33, and 8 respectively. This is in agreement with later experience in showing that little protection is to be expected from one dose. Among the uninoculated there was one death in every 7.8 cases, while among those receiving three doses there was not only a lower morbidity but only one death in every 36 cases.

Kuhn¹³ concluded that the immunity was largely lost after one year, since after that time there was little difference between the sick and death rates of the vaccinated and unvaccinated.

¹² Shoemaker: Herero Campaign, International Clinics, Phil., 19 S., 1909, ii.

¹³ *Ibid.*

Col. Firth,¹⁴ R. A. M. C., reasoning from similar data, found that the vaccines in use to-day in India, maintain a high degree of protection for at least two and one-half years.

The history of antityphoid vaccination can be divided into two stages. The first period includes the early experimental work of Pfeiffer, Kolle, Wright, and Wright's immunization of 4,000 men of the British Indian Army, the Boer War and the German campaign against the Hereros. The most accomplished during this period was the reduction of the morbidity to about one-half among the vaccinated and a rather greater diminution of the case mortality.

EXPLANATION OF EARLY FAILURES

Disappointment at the poor showing made by antityphoid vaccination during this first period was widespread, and for a time prevented any serious consideration of its further use. The loss of interest was due to two things; first, the undoubted failure to secure anything like absolute protection against infection and death, and second, what was perhaps even more important, Wright's unfortunate doctrine of a negative phase. To consider first the failure to secure a high degree of protection; we now know from the writings of Col. Leishman,¹⁵ that much of the vaccine sent to South Africa, was, from our present point of view, over-heated in its preparation or otherwise rendered inert. Later investigations by Col. Leishman, Majors Harrison, Grattan and others, have shown that over-heated vaccines are almost worthless. Poor and incomplete immunity due to faulty vaccines, is therefore, a preventable condition, and this source of error once known, its avoidance and the regular production of efficient, powerful vaccines is a simple matter.

WRIGHT'S DOCTRINE OF THE NEGATIVE PHASE

The other cause of disappointment and lack of interest was the doctrine of the negative phase. The doctrine that vaccina-

¹⁴ Jour. Roy. Army Med. Corps, 1911, xvi, 589.

¹⁵ Harben Lecture, Anti-typhoid Vaccination, Jour. Roy. Inst. Pub. Health, Lond., 1910, July, August and September.

tion could actually and materially increase one's susceptibility to infection for a time, was generally believed, and was advocated by none more emphatically than by Wright himself. It mattered not that experience with other vaccines had shown no increase of susceptibility beyond the normal. Wright built up the theory of a dangerous negative phase upon very questionable determinations of the opsonic index and upon certain phenomena observed in the production of diphtheria and tetanus antitoxin in animals. It is well known that the antitoxin content of the blood of the animals used will fall from a previously high level after each administration of toxin. The conditions, however, are not at all comparable; in human beings no such enormous doses are used, and further, in the beginning of the immunization of a horse, when the doses are small and widely spaced, it is doubtful if there be any reduction of resistance below the normal level. Upon such theoretical grounds and upon isolated instances of severe typhoid fever following immediately after vaccination, was this doctrine built up, and very curiously, it was uncritically accepted by the greater part of the medical world. Wright even went so far as to discover a condition of increased susceptibility to smallpox immediately following vaccinia. However, vaccination against smallpox in the presence of an epidemic was too firmly rooted to be successfully questioned. The doctrine of the negative phase in practical immunization appeared only in relation to typhoid fever; nothing was heard of it at that time in connection with bubonic plague and cholera, except from Wright.

In an article published by him in 1902,¹⁸ on the results of vaccination in South Africa, the following can be found. "In bringing this summary to a conclusion, I am anxious to re-emphasize a point already emphasized by me in previous papers; that there is, in connection with all protective inoculations, a risk to be considered. There is the risk that, (a) in the case where the patient's resistance is naturally low, or has been reduced, as is often the case, by a previous attack of typhoid fever, (b) in the case where the patient is inoculated with a

¹⁸ Lancet, Lond., Sept. 6, 1902, 654.

full dose of vaccine in actually infected surroundings, and (c) in the case where the patient is inoculated with an excessive dose, or is reinoculated too soon, the system may be left more open to infection at a period when it stands in need of protection. The facts . . . seem to me to indicate the reality of this risk."

In a hasty search through the later publications of Wright, very few definite statements can be found to justify his former attitude. In later papers he speaks quite guardedly; observing that "the risk of a negative phase comes seriously into consideration, only when excessive doses of vaccine are employed, or when the prophylactic inoculations are undertaken in the actual presence of infection."¹⁷ He adds that the remedy lies near at hand and consists of a reduction in the size of the dose.

In the preface to his book, *Studies on Immunization*, published in 1909, he no longer insists on the dangers of increased susceptibility, but speaks of the practicability of controlling the negative phase, and of immunizing a patient, without risk or appreciable delay. He even goes further, and approves the therapeutic use of antityphoid vaccine; a position which would have been absurd if vaccination lowered the patient's resistance to typhoid toxins.

The best discussion of the subject from the opposite point of view, we owe to R. Pfeiffer,¹⁸ who questioned Wright's data, based as it was principally upon the opsonic index. Pfeiffer and Friedberger convinced themselves that guinea pigs, inoculated with large doses of vaccine, did not show any increased susceptibility to intraperitoneal infection with living cultures, but on the contrary, their resistance was distinctly increased, and that this change was apparent within a few hours. This increase of resistance continued to be present up to the time when the formation of specific antibodies began. These results are in agreement with the earlier work of Pfeiffer and Isaeff on non-specific resistance as contrasted with specific immunity.

¹⁷ Wright's *Studies on Immunization*, Lond., 1909, and Boston M. & S. J., May 9, 1903.

¹⁸ Centralbl. f. Bakteriol., 1 Abt., 1908, Referate, xl, 712.

What can be said on the practical side of the question? Is it true in actual practice that vaccination increases susceptibility to infection? A definite and conclusive negative answer can be made to these questions. Leishman¹⁹ relates his experience in inoculating 100 attendants at the Barming Asylum, in Maidstone. There, if ever, evidences of increased susceptibility would have been present. The inoculations were made at the height of the epidemic, with doses of vaccine considerably larger than are now used. Yet no single case occurred and Leishman was convinced that the dangers of a negative phase were more theoretical than real.

Cullinan,²⁰ in 1901, vaccinated 500 persons, at the Richmond Asylum, Dublin, during an epidemic lasting five months, and among these, only 1.36 per cent contracted the disease, and almost all were in the incubation stage when inoculated; on the other hand, of the 114 uninoculated nurses, 14.9 per cent became infected.

More recently Spooner, in Boston,²¹ and Hachtel and Stoner²² in Baltimore, have immunized the personnel of the Boston and Baltimore Hospitals. This is, of course, equivalent to vaccinating in the presence of an epidemic; yet they detected no indication of increased susceptibility immediately following vaccination.

Spooner²³ has recently used vaccine during an epidemic with satisfactory results. He writes as follows: "The water supply of a limited number of people in a small Vermont village became contaminated with the typhoid organism from the excreta of an isolated individual who had died from the disease six months prior to the epidemic. The original primary cases, seventeen in number, appeared simultaneously. Within a week,

¹⁹ Harben Lecture, September, 1910.

²⁰ Cullinan, H. M.: Anti-typhoid vaccination during an epidemic in Dublin, reported by Wright, Brit. Med. Jour., Oct. 26, 1901, 1226.

²¹ Ztschr. f. Hyg. u. Infektionskrankh., Leipz., 1894, xvii, 355; Jour. Am. M. A., 1912, lix, 1359.

²² Jour. Am. M. A., 1912, lix, 1364.

²³ Trans. Assc. Am. Phys., 1912, xxvii, 343.

twenty-nine of the remaining forty-eight who had been exposed to the disease through the water supply had been inoculated; nineteen remained uninoculated. Among the latter, five cases developed; among the former, one. This case presented his first symptoms immediately following the first dose of vaccine, and the disease ran a mild course."

The immunization of those in the immediate neighborhood of typhoid fever patients brings up this question in acute form. We have, so far as possible, immunized all contacts and have seen only good results. Many, however, still hesitate to practice in typhoid fever what is regularly done in the case of variola.

Peterson ²⁴ relates the following: "An interesting fact, which in my mind removes any doubt of its efficacy, was that in one house, there were fourteen occupants, seven of these were in the acute stage of typhoid. The remaining were immunized with no further development of typhoid in the house. The house and surroundings were about as unsanitary as any I ever saw or expect to see."

As we now look back upon this dark period, we can see that the unfortunate doctrine of a harmful negative phase arose in part at least, from a false interpretation of the relative failure of vaccination in South Africa. That failure we now believe was due, not to any false or dangerous element in the principles of prophylactic vaccination, but to the use in improper dosage of an over-heated and comparatively inert vaccine which simply failed to give the desired protection.

Leishman and his co-workers discovered the fault and found the remedy. They reduced the amount of heat used in killing the cultures, and also diminished the dose. At Aldershot they tried out various doses upon human beings and adopted that now used in practically all countries, 500 and 1,000 million bacilli; as this quantity was sufficient to produce an abundance of immune bodies and rarely caused severe reactions.

The doctrine of a negative phase was so simple, so reason-

²⁴ Peterson, J. J.: Control of Typhoid Fever by Vaccination, Southern Med. Jour., 1912, v, 257.

able, and if true, so important for every one to know, that it came early to the knowledge of all reading physicians. Backed as it was by abundant statistics from South Africa, it was accepted as true by almost every one, and its overthrow has not yet been fully accomplished. In England and in India, little of it is now heard; in this country, in the army and in the navy service, its conquest dates back only three years. In civil life we still hear it referred to by men who have not yet used antityphoid vaccine. Owing to this doctrine, there is, in France, at the present time, and has been for the past two years, both in the Academy of Medicine and in the Army, an active and energetic opposition to the use of vaccination in the Military and Naval Services.

My personal experience with antityphoid prophylaxis began, as I have stated, in 1908, when I was ordered abroad by the War Department to study the subject at first hand. In Col. Leishman's laboratory in London, I found that vaccine was prepared by growing in broth a single selected strain (Rawlings) of the typhoid bacillus. The flasks used were long flat bottles which were incubated lying on their sides, giving a thin layer of medium in contact with the air. The bottles of broth, after preliminary incubation to determine their sterility, were inoculated with a pipette from a broth culture. After 24 to 48 hours incubation the growth was usually sufficiently heavy to require the addition of a small quantity of plain broth to reduce the bacterial count to the quantity desired; 1,000 million to the c.c. The counting was done by an ingenious wet method devised by Harrison, using washed red blood cells from a definite quantity of blood, with which to compare the number of bacteria in an equal quantity of emulsion. The vaccine was killed by heating for one hour at 53° C. and after cooling, 0.4 per cent. of lysol was added as a matter of safety.

The English vaccine is, therefore, a killed broth culture made from a single strain of the bacillus, which was originally selected because it emulsified well from agar slants. Preliminary trials of this organism showed that it agglutinated well in immune serum and produced in good quantities all measurable kinds of

antibodies in animals and man. This strain is still in use in England and in our own service; and although we have searched from time to time for a strain with greater antigenic properties, none has yet been found.

In Germany the only prophylactic used at all extensively was made according to the method of Pfeiffer and Kolle. Aside from their use of agar media, the characteristic of the vaccine is its standardization by the loop method; a normal loop being one which holds 2 m. gr. of fresh bacterial substance. Experience showed that a single slant would furnish about ten normal loopfuls, and that the quantity of vaccine obtained per test tube was 5 c.c. This enables us to compare the dosage with that used by the English and ourselves, since we obtain from 15 to 20 c.c. of prophylactic per tube. The German dosage was therefore, about three to four times as great. Their method of killing and the temperature used are also important for a complete understanding of their vaccine. They, also, used a single strain of the bacillus; the culture, known as 151, was selected from a large number because of its exceptional binding properties. Wassermann, particularly, has insisted that the property of binding and of producing antibodies is of more importance in the selection of an organism for the production of vaccine than its virulence.

Our own vaccine is made from a single strain of bacillus, (Rawlings), and the culture is grown on agar in flasks for eighteen hours. At first, when small quantities only were needed, test tubes were used, but as the quantities increased Kolle flasks were substituted; each with an agar surface equivalent to twelve tubes.

The culture used is plated out, a dozen colonies are fished on to double sugar tubes²⁵ and from these, macroscopic agglutinations are made. Any culture which fails to develop the characteristic appearance on double sugar, or to give a good agglutination, is discarded; from the remaining cultures, agar slants are inoculated and the next day emulsified in a little broth;

²⁵ Russell, F. F.: Jour. Med. Research, Boston, 1911, xxv, 217.

and with this thick emulsion the Kolle flasks are inoculated by means of a large swab. If they show no contamination after eighteen hours incubation, the growth is washed off in a little salt solution, and while a sample is being counted, the thick suspension is heated in large flasks in a water bath for one hour at 53° to 54° C.

The killed vaccine is diluted with large quantities of salt solution until the desired concentration, 1,000 million to the c.c., is obtained. Finally one-quarter per cent of tricresol is added as a matter of safety. After aërobic, anaërobic and animal tests have been made, the vaccine is put up for shipment, in hermetically sealed ampuls of normal glass.

The aërobic and anaërobic tests for sterility are made with large quantities of vaccine, several c.c. to each tube and plate; the animal tests consist in the inoculation of a mouse and guinea pig, with 0.5 and 1.5 c.c. for the exclusion of tetanus spores, and a rabbit with three doses at ten-day intervals to determine the immunizing power of the vaccine. The average titre of the agglutinating rabbit serum obtained with the last eighteen batches of vaccine after thirty days was 1 to 18,000.

Morphological tests of purity, using Gram's stain, are made at each stage of preparation, and a few lots of vaccine have been discarded because of contamination with the *B. subtilis* group; but none have ever been rejected because of the animal tests. They are continued, however, because of the occurrence of a number of deaths from tetanus in India after the administration of plague vaccine. In one case a batch was discarded because it failed to produce good agglutinations in the rabbit test.

We have used agar cultures because of the ease of detecting contamination, and to avoid the injection of extraneous materials contained in fluid media.

The vaccine is killed by heat rather than by chemicals, using the least amount possible to obtain sterility, and it is protected against subsequent contamination by tricresol.

Our vaccine is essentially the whole body of the *bacillus typhosus*, changed as little as possible in killing, suspended in a convenient quantity of salt solution. Such a vaccine has the

merit of simplicity, is readily and easily prepared and constant in quality.

What then have been the results obtained with it in protecting human beings?

We began to use the prophylactic early in 1909, after first submitting the project to a board of officers selected from among the distinguished members of the Medical Reserve Corps of the Army, since it was realized from the start, that little could be accomplished without the support of the medical profession of the country. This board recommended the introduction of voluntary vaccination and work began in earnest early in 1909.

All who had seriously studied the subject of bacterial vaccines and typhoid immunity, realized that the use of prophylactic inoculation was theoretically possible and justifiable, but few considered it practical. For the Army, however, the question was too important to be slighted, and a repetition of the experiences of the Spanish War must be prevented in one way or another.

Antityphoid vaccination was taken up with a firm conviction as to its value, but with many misgivings as to our power to convince others, or to secure enough volunteers to give it a fair trial. It is difficult to overcome the inertia of great bodies like the Army, and there is always the danger of ignorant and malicious criticism.

The first doses, given to the laboratory staff, seemed to have a greater importance, and the operation was more momentous than the occasional therapeutic use of other vaccines, since so much depended upon an auspicious beginning.

When the immunization of the laboratory force had been completed, available volunteers seemed for a time to have been exhausted; but the news spread and practically all of the medical officers in and about Washington volunteered, and in turn, sent their wives and children, friends and servants. This helped us over the first obstacle and we began to obtain volunteers from the Hospital Corps. By the end of 1909, 1,887 persons had received the prophylactic treatment, and during the next year, 1910, 16,073 additional volunteered. During the

first part of 1911, volunteers continued to present themselves in increasing numbers, so that immunized men came to be present in practically every garrison in the United States proper. The measure was no longer strange to the Medical Corps, nor to the enlisted personnel of the Army. We noticed, however, as with all voluntary measures, that there was great inequality in different garrisons, depending, of course, on the interest and enthusiasm or opposition of the Commanding Officer and the Surgeon. Such conditions are inseparable from voluntary measures. In the Department of the East where the measure was actively pushed by the Chief Surgeon, Col. John Van R. Hoff, more volunteers were obtained than in all other departments together. Lectures and missionary work among the officers were resorted to; as we early saw the truth of the well known fact, that the men follow cheerfully wherever the officers lead.

One Commander, finding typhoid present in his garrison, and epidemic in the neighborhood,²⁶ succeeded in having the entire regiment vaccinated, by refusing permission to leave the limits of the military post to any one not protected against typhoid by vaccination or attack of the disease.

It is understood that in India, volunteering was encouraged by refusing the opportunity, so dear to the soldier, of active service, to regiments whose quota of inoculated was small. Such incidents merely show the difficulty of protecting the health of a community which refuses to accept or to interest itself in measures for its own welfare.

In the English service, vaccination against typhoid has always been, and still remains, a voluntary measure; but we, in March, 1911, introduced unequivocal compulsion, on the occasion of the mobilization of a Manceuvre Division in Texas.

In the Army, the duty of the physician is, of course, as in civil life, to treat the sick and minister to the wounded in the best and most approved fashion; but the military surgeon has, beside, another duty, more important by far than the

²⁶ Lyster, Mil. Surgeon, 1911, xxviii, 528.

humanitarian one referred to; it is the duty of preserving the health of all under his charge and of having, at all times, the maximum number of able-bodied men on the firing line, and of keeping them healthy enough to remain there. With this duty clearly before us, compulsory vaccination against typhoid was recommended for every person in the Division, not already protected by an authenticated attack of typhoid, or by recent vaccination.

At this time, we had already obtained records of vaccinations of approximately 20,000 persons, and knew that the preparation we were using was harmless; we knew too that it caused very few severe reactions in healthy persons; and that no vaccination, however severe the immediate reaction may have been, had been followed by permanent injury to the individual; and further, that by all possible laboratory tests, the immunity conferred was identical with and equal to that remaining after typhoid fever. Statistics of typhoid among vaccinated and unvaccinated troops were beginning to confirm, on a large scale, the laboratory tests.

It was impracticable, from the data at hand, to give accurate statistics comparing the rate among the vaccinated with the unvaccinated; but enough had been learned for our purpose. It was necessary to protect that body of 20,000 men against typhoid, as well as against smallpox and other infectious diseases. We were convinced that this could best be done if every man, not already protected, were vaccinated, and a recommendation to this effect, from Surgeon General Geo. H. Torney, was approved by the War Department and vaccination ordered on the ninth of March, 1911, for all troops on the border.

There is an apparent basis for objection to compulsory vaccination in typhoid fever, based on the reasons for universal vaccination against smallpox. In smallpox susceptibility is universal, and no other measure of sanitation or protection gives immunity. It is vaccination or nothing. With typhoid fever, under ordinary conditions, the problems presented are decidedly different. Not every one is susceptible. During the Spanish War,

Reed, Vaughan, and Shakespeare ²⁷ showed that one-fourth to one-third of those exposed contracted the disease.

Susceptibility to infection is, therefore, much less than with smallpox. And further there are other good and practicable methods of prevention. Pure water, good sewerage and supervision of milk and other food supplies, properly carried out over a long series of years, will cause this disease practically to disappear, as it has in many parts of England and Prussia. This is well known and is a condition we are looking forward to in our own country. Improved sanitation in the large cities is constantly reducing the typhoid death rate and under such circumstances, neither compulsory nor voluntary vaccination need be considered. The conditions with which we have to deal, in actual or mimic warfare, are so entirely different that one can scarcely recognize the highly contagious disease which absolutely paralyzes regiments, divisions and armies as of the same nature as the sporadic typhoid of cities. We cannot forget that typhoid fever is proteus-like in the variety of its disguises.

The following table shows the havoc wrought by typhoid fever in some modern wars:

TABLE IV.

	Strength	Typhoid Cases	Typhoid Deaths	Killed in Action or Died of Wounds	Died of Disease	Wounded	Missing
Franco-German War, German Army.....		73,393	6,965	28,268	15,240	68,498	12,854
Spanish-American War, American Army.....	107,973	20,738	1,580	243	2,565	1,445	
Boer War, British Army...	380,605	57,684	8,022	7,702	13,250	22,829	
Russo-Japanese War, Russian Army.....		17,033		34,000	9,300	141,800	

We can all remember the experience of 1898 in military camps; it is well to review a few of the points brought out so

²⁷ Abstract of Report on the Origin and Spread of Typhoid Fever in U. S. Military Camps during the Spanish War of 1898. Washington, Government Printing Office, 1900, 191.

clearly by Reed, Vaughan and Shakespeare ²⁸ lest we forget the lessons of experience.

They found that typhoid fever appeared in over 90 per cent of volunteer regiments within eight weeks of going into camp, and in some regiments of regular troops, it appeared in three to five weeks; that it appeared both in small and large encampments, in the Northern as well as the Southern States. They stated their belief that "with typhoid fever as widely disseminated as it is in this country, the chances are that if a regiment of 1,300 men should be assembled in any section and kept in a camp, the sanitary conditions of which were perfect, one or more cases of typhoid would develop."

They observe that typhoid fever is more likely to become epidemic in camps than in civil life because of the greater difficulty of disposing of the excretions of the human body. A man infected with typhoid fever may scatter the infection in every latrine in his regiment before the disease is recognized in himself.

They demonstrated that water was not an important cause of the spread of the disease, and that flies undoubtedly served as carriers of the infection; that the spread was through contact and was characterized by a series of company epidemics, each having more or less perfectly its own individual characteristics.

They showed that an organization once infected continued to produce new cases, even though it changed its camp site, or travelled long distances by land or sea. This doctrine, radical at the time, has since been made simple, through the discovery of temporary and chronic bacillus carriers.

In this war the mortality from typhoid fever was 86.24 per cent of the total. The morbidity was 192.65 per thousand of mean strength, or a little less than one-fifth. The mortality per thousand of mean strength was 14.63.

When orders were suddenly issued in the spring of 1911 for the mobilization in Texas, California and along the Mexican frontier of the largest body of troops in the field since the

²⁸ Ibid.

Spanish War, the question of typhoid prophylaxis ceased to be academic and became a practical question insistent on solution. The mobilization plans did not provide for fixed camps, where water supplies and even sewerage systems might have been arranged, but called for active service in the field, under conditions simulating, as closely as possible, actual warfare. Indeed, we did not know but that a campaign into Mexico might not follow quickly the assembling of the troops. Even the incinerators, recently used in manœuvre camps, for the destruction of excreta by fire, were forbidden, as being too heavy and cumbersome and too expensive to form part of the equipment of moving troops.

Experience during the Spanish War had taught us what to expect in large and protracted camps. In eight weeks we felt certain, through the agency of flies, dust and the inevitable close contact of crowded camps and more crowded tents, that we would have some cases of typhoid, and was it probable that the advances in field sanitation could be relied upon to protect us against a repetition of that war's disasters? Although conditions could not have been expected to have been as bad as in 1898, there would likely have been typhoid fever enough to have handicapped some portion of our small force had an advance across the border become necessary.

With these possibilities in view and with complete confidence in both the effectiveness and harmlessness of antityphoid vaccination, you can well understand why in the opinion of the Surgeon General, compulsory vaccination was to be preferred to the half-way measure of volunteering.

The results fully justified the position taken. The Manœuvre Division, as it was called, was ordered to mobilize in Texas, California and along the Mexican border in March, 1911. They remained in camp and on the border patrol for a period of four months, when the greater number were returned to their garrisons. A few thousand men had already received the prophylactic, the others were vaccinated as rapidly as they arrived. The vaccine was prepared at the laboratory of the Army Medical School in Washington, and shipped as rapidly

as it could be used. During the thirty days after the receipt of orders, approximately 60,000 doses were prepared and delivered. As the full course of three doses occupies twenty days, we had no great difficulty in supplying the vaccine as rapidly as it was needed.

In addition to the main divisional camp at San Antonio, smaller camps occupied by separate brigades were established at Galveston, Texas, and San Diego, California. At Galveston there were about 4,500 persons, and at San Diego 3,000. No cases of typhoid were reported among the troops in Galveston, although the Chief Surgeon estimated that there were 192 cases among the civil population of the city during the period of the encampment. From San Diego only two cases ²⁹ were reported, and one of these was doubtful. Other detachments, smaller in size, were scattered along the border, yet there was no typhoid. The camp in San Antonio was the largest and best known of the manœuvre camps, and the interest of the public had centred upon it. For a period of four months, beginning in March, almost 13,000 troops were located there, and any one who visited it knows that all the elements which tend to affect the health of men under canvas, were controlled better than they had ever been before. The sanitary difficulties of camp life arise mainly from the lack of established water, sewer and scavenger systems and these difficulties were overcome at San Antonio by new, and ingenious, yet practical expedients. Flies, the cause of so much trouble in 1898, were kept down to a minimum by a series of simple, yet effective company crematories. In drawing a mental picture of a military camp, one is quite apt to overlook the necessary camp animals; at San Antonio, for instance, there were 6,000 horses and mules, scattered here and there in close proximity to the quarters of the men and the proper disposal of the stable refuse by fire was, in itself, no small undertaking.

We can best judge of the combined effects of vaccination and sanitation by comparing this camp with the one located at Jacksonville, in 1898.³⁰

²⁹ Annual Report, Surgeon General, U. S. Army, 1912, 51.

³⁰ Kean: Jour. Am. Med. Assn., 1911, lvii, 713.

TABLE V.
1898, SPANISH WAR, CAMP AT JACKSONVILLE, FLORIDA.

Number of troops	Cases of typhoid, certain	Certain and probable	Deaths, typhoid	All deaths
10,759	1,729	2,693	248	281
12,801	2		0	11

At Jacksonville, there were assembled 10,759 men, among whom there were 1,729 undoubted cases of typhoid; and including those in which a diagnosis of typhoid was probable, there were 2,693 cases with 248 deaths. This camp lasted approximately as long as the camp at San Antonio in 1911; both camps were situated in about the same latitude and each had artesian well water of excellent quality, yet in 1898 there were over 2,500 cases of typhoid fever with 248 deaths, and in 1911 only two cases with no fatalities.³¹

We know that the immunity was not due to lack of exposure, since there were reported to the health office, 49 cases of typhoid fever with 19 deaths, among the civil population of the city of San Antonio.

Our men were not rigidly confined to camp but had leisure and opportunity to visit the neighboring cities of San Antonio and Galveston. Thousands of soldiers spent more or less time in these cities, where they ate, drank, and slept; in fact, became for the time being, a part of the community. In Galveston, especially, where a ten minute ride carried one from camp to the heart of the city, the number of men visiting town was large. The soldier is not over particular where he obtains food and drink; restaurants, good and bad, lunch wagons, street corner stands, all have his patronage. Fruits and pastry and sweets were purchased of hucksters lined up along the camp boundaries. The best kind of camp sanitation alone could not have prevented typhoid in the presence of all these possible chances of infection,

³¹ Annual Rep., Surgeon Gen., U. S. A., 1912, 51.

with the disease as prevalent as it was in the adjoining cities. What it did do was to reduce the number of chances of infection, and prevent the appearance of secondary cases from the two which actually occurred.

Many other striking illustrations of the efficacy of vaccination might be instanced; one, however, must suffice.³² A cavalry regiment of about 700 men engaged in a twenty-one day practice march through a part of Tennessee, where typhoid fever is endemic throughout the year. During their march of 600 miles, there was no attempt to boil or sterilize the drinking water. The amount of sickness was practically nil, and no cases of typhoid developed. Following a previous practice march in the same region, ten cases occurred, and the further spread of the disease, at that time, was finally stopped by wholesale vaccination.

Compulsory vaccination in the southern manœuvre camps was ordered on March 9; the next step, June 9, 1911, was the extension of the order to all recruits; since which time 2,000 to 3,000 recruits have received the prophylactic treatment each month, at the same time being vaccinated against smallpox. If the vaccinia be severe, the second dose of the typhoid prophylactic is postponed a few days, but in no other way has it been necessary to deviate from this routine of simultaneous vaccination against the two diseases. The two vaccinations are completed by the time the man has been 20 days in the service. It is our present practice to revaccinate against both smallpox and typhoid at the beginning of each four year period of enlistment. This is not because the immunity has by that time disappeared, for its duration is not yet known. It no doubt diminishes gradually, as in the case of smallpox, yet in the service, it is desirable to maintain the Army in a maximum state of protection against infection at all times, and it does not seem wise to omit vaccination until an outbreak of typhoid shows the disappearance of all immunity. Smallpox has been almost entirely suppressed; there were only five cases among

³² Lyster, Military Surgeon, 1911, xxviii, 528.

American troops in 1911, with no fatalities, and typhoid has ceased to be the scourge of former days.

The next and most important step was the extension of compulsory prophylaxis to all persons in the service under forty-five years of age; and this was ordered on September 30, 1911. In the United States proper the order was not fully executed before the first of January, 1912. In the Philippines, it was not carried out until the first part of the present year.

If vaccination gives the protection we believe, its good effect should show in the total number of cases reported in the Army year by year, and the following table and charts have been arranged to show these facts:

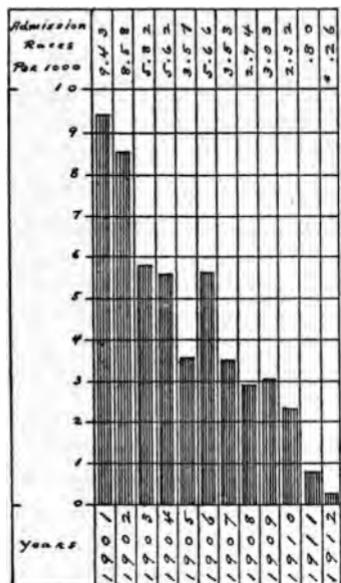


FIG. 1.—Admission rates for typhoid fever, United States (enlisted men).

* All information available in the Surgeon General's Office, Jan. 10, 1913. Later reports may show additional cases. Strength only approximate, as it was not possible to obtain a true strength on Jan. 10, 1913.

Antityphoid vaccination begun voluntarily in 1909 was made compulsory in 1911.

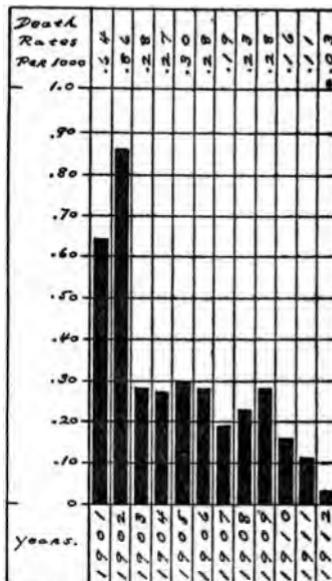


FIG. 2.—Death rates for typhoid fever, United States (enlisted men).

* All information available in the Surgeon General's Office, Jan. 10, 1913. Later reports may show additional cases. Strength only approximate, as it was not possible to obtain a true strength on Jan. 10, 1913.

Antityphoid vaccination begun voluntarily in 1909 was made compulsory in 1911.

TABLE VI.
TYPHOID FEVER—UNITED STATES. ENLISTED AMERICAN TROOPS.

Year	Mean strength	Abso- lute cases	No. deaths	To each 1000 soldiers, of the command, the ratios are	
				For cases	For deaths
1901	26,515	250	17	9.43	.64
1902	39,736	341	34	8.58	.86
1903	42,264	246	12	5.82	.28
1904	43,940	247	12	5.62	.27
1905	42,834	153	13	3.57	.30
1906	40,621	230	12	5.66	.28
1907	35,132	124	7	3.53	.19
1908	46,316	136	11	2.94	.23
1909	57,124	173	16	3.03	.28
1910	55,680	129	9	2.32	.16
1911	55,240	44	6	0.80	.11
1912	58,119	15	2	0.26	.03

Note.—This includes all information available in Surgeon General's Office, to April 1, 1913. Strength for officers and enlisted men for 1912 is only approximate, as it was not possible to obtain a true strength on that date.

Table to show the number and proportion of typhoid fever cases contracted before enlistment, and among the protected (United States proper only) Officers and enlisted men:

TABLE VII.

Year	Total cases	Total deaths	Infected prior to enlist- ment	Among the vaccinated	
				Number of cases	Number of deaths
1909	173	16	?	1	0
1910	129	9	?	4	0
1911	44	6	?	7	0
1912	18	3	5	6	0

From these figures and charts the deductions would seem quite clear. They are based upon accurate observations of from 70,000 to 80,000 men each year, and are as accurate as only great care can make them. We see a sudden drop in both morbidity and mortality during the last two years, which corresponds with

TABLE VIII.

TYPHOID FEVER, 1901-1911, FOR THE WHOLE ARMY, OFFICERS AND ENLISTED MEN, AT HOME AND ABROAD.

Year	Mean strength	Cases		Deaths			Occurring among those who were vaccinated
		Number of	Ratios per 1000 of mean strength	Number of	Ratios per 1000 of mean strength	Percentage of total cases	
1901	81,885	552	6.74	74	.88	13.0	
1902	80,778	565	6.99	69	.85	12.2	
1903	67,643	348	5.14	30	.44	8.6	
1904	67,311	293	4.35	23	.33	7.8	
1905	65,688	206	3.14	20	.30	9.7	
1906	65,159	373	5.72	18	.27	4.8	
1907	62,523	237	3.79	19	.30	8.0	
1908	74,692	239	3.20	24	.31	10.0	
1909	84,077	282	3.35	22	.26	7.8	1 0
1910	81,434	198	2.43	14	.17	7.1	7 0
1911	82,802	70	.85	8	.10	11.4	11 1
1912	88,478	27	.31	4	.044	14.8	8 0

the increase in the use of a prophylactic immunization during the same period.

Since the Spanish War, medical officers of the Army have given much attention to the prevention of this disease and have greatly reduced the frequency of its occurrence. The greatest care, however, in sanitation and hygiene did not appear to be successful in reducing the number of cases much below 150 per annum in the United States, for the present strength of the Army; or an average number of not quite three cases to every thousand men.

The importance, for statistical purposes, of the year 1912, arises as you see, from the fact that not until then did we have complete statistics for a calendar year, covering compulsory immunization of the entire Army. All previous tables were based upon either voluntary immunization of small numbers, or mixed voluntary and compulsory immunization, and such tables were always open to the objection that volunteers constitute a group of thoughtful, careful men, who would naturally be less liable to infection than the rank and file of the Army. This

objection is once and for all disposed of by the compulsory use of typhoid prophylactic, and the year 1912 demonstrates fully what may be accomplished when the measure is used fearlessly and regularly upon a large number of persons.

In the Navy ³³ "the compulsory use of typhoid prophylactic was inaugurated on January 1, 1912, and the inoculation of practically the entire naval personnel has been completed without a single serious result or casualty. Only a small fraction of one per cent had reactions necessitating rest in bed, and but a small percentage of individuals required to be excused from duty. As this policy has been put into effect so recently, it is impracticable to formulate any comparative data relative to the rate of the disease, but reports, made in response to a bureau circular letter, show that, in men who had received the three injections, only one authentic case of typhoid fever has occurred, although three were reported as such in which laboratory findings failed to verify the diagnosis. One mild case occurred in a man who had but two inoculations. One officer known to be a typhoid carrier, was found to be free of the typhoid bacillus subsequent to receiving the three injections required. The prophylactic administered to the personnel on the Asiatic station was prepared at the Naval Hospital, Canacao, P. I."

All other antityphoid vaccine used by the Navy was prepared in our laboratories at the Army Medical School.

The following table shows the amounts of vaccine furnished from the Army Medical School, for the use of the Army, Navy, Militia and others.

TABLE IX.

Year	Army	Navy	Militia	Others	Total
1909	c.c. 6,000	c.c.	c.c.	c.c. 1,000	c.c. 7,000
1910	68,592	7,251	75,843
1911	237,540	50,000	22,241	6,692	316,473
1912	147,463	187,284	28,751	11,218	374,716
	459,595	237,284	50,992	26,161	774,032

³³ Annual Report, Surgeon General, U. S. Navy, 1912, 16.

ESSENTIALS FOR A TYPHOID VACCINE

The essential requirements for a prophylactic vaccine are that the immunization shall be harmless, that the process shall not be attended with unpleasant symptoms; that the immunity shall be reasonably long.

In addition, the vaccine, to be of real service, must be available in ample quantity at short notice; which means, of course, that the vaccine must either be stable enough to withstand long storage, or that the method of preparation be so simple that unlimited quantities will be available on very short notice, for use in epidemics and among troops upon mobilization.

That the immunization is harmless is sufficiently clear, since about 200,000 men, as nearly as we can estimate, have already been immunized with our vaccine, without a single fatality, or serious complication.

At San Antonio, one case of musculospiral neuritis was apparently directly due to the vaccination. Our directions distinctly call for a subcutaneous inoculation, as slow rather than rapid absorption is desired; yet some physicians persist in giving deep hypodermics, as was evidently done in this case.

At Guantanamo, Cuba, in 1911, one case occurred which has aroused some comment.³⁴ A private of the Marine Corps received one dose of vaccine. He felt perfectly well at the time and previous to the inoculation. Two days later he was admitted to the hospital, acutely ill with high fever (104°), headache and dulled intellect. Within twenty-four hours after admission he began to grow rapidly worse. He died seventy-six hours after admission and seven days after vaccination. The autopsy record, and examination of the ileum, preserved at the Naval Medical School, show clearly that the man, at the time of his death, was at the end of the second or beginning of the third week of the disease. His infection was, therefore, at least a week old when the single dose of vaccine was given. Whether or not it affected his condition it is impossible to know. Cer-

³⁴ U. S. Naval Bulletin, 1911, v, 336, Freeman, Southern Medical Journal, 1912, v, 4.

tainly one is not justified in drawing any inference as to the harmful effects of vaccination from a single case, and that an ambulatory one, since walking cases are notorious for the late intensity of symptoms and high mortality.

It is not very unusual to read in public prints of fatalities following vaccinia, and a recent instance, reported by Broeckerhoff,²⁵ is quite comparable to the Guantanamo case. A nine-year-old boy was vaccinated against smallpox on the seventh of May; at the time he fainted and was sent home in the company of some other boys. On arrival he was pale and complained of pains and headache, and went to bed immediately. The physician who saw him reported the vomiting of blood and the presence of dark blood in the stools. There was no appreciable rise of temperature, the pulse was small and rapid. There was no morbid change at the site of vaccination. On the ninth he died, without developing any new symptoms. The autopsy showed definitely that the cause of death was hemorrhage from typhoid ulcers, and that the vaccinia was in no way responsible for his death.

In this connection it is necessary to remember that we never administer the prophylactic to any but the healthy. If there be any doubt about possible illness the treatment is postponed until a diagnosis can be made.

We also know that, except in rare instances, the immunization is not attended with unpleasant symptoms. When the practice was first introduced, careful records of all general reactions were kept and the following table shows the rarity of severe general reactions, in over 97 per cent of persons the general reaction was mild or absent.

Severe reactions occurred in only one to three persons per thousand, and the experience of the Navy, using our vaccine, is confirmatory of our own.

The degree of immunity is, of course, not absolute, since twenty-seven cases (including eight so far reported for 1912), with one death from hemorrhage, have been reported during the past four years.

²⁵ Centralblatt f. Bakteriol., 1 Abb., Ref., 1912, iv, 549.

TABLE X.
TO SHOW DEGREE OF SEVERITY OF GENERAL REACTIONS.

Dose	Number of doses	Per cent absent	Per cent mild	Per cent moderate	Per cent severe
First dose.....	45,680	68.2	28.9	2.4	0.3
Second dose.....	44,321	71.3	25.7	2.6	0.2
Third dose.....	38,902	78.0	20.3	1.5	0.1
Total.....	128,903

In the light of our experience with vaccinia, it is improbable that we shall ever obtain an immunization process which will give absolute immunity. There is an individual variation among persons just as among animals. In the laboratory it is not unusual to find certain animals refractory to immunization, and we cannot expect more uniformity among human beings.

The Army is as well protected against smallpox as repeated vaccination can make it, yet we had, in the entire Army, American and native troops, 21 cases in 1908, 7 in 1909, 17 in 1910, and 20 in 1911, a total of 65 cases with two deaths in four years, against 27 cases of typhoid fever with one death, after antityphoid vaccination in an equal length of time.

The duration of the immunity following our method of prophylaxis has not yet been determined. The interval between vaccination and the onset of typhoid fever in the twenty-seven cases referred to is as follows:

In only four instances, in the 27 reported cases, is the interval between vaccination and infection less than one month; should any one feel inclined to interpret these infections as instances of a negative phase, they would also serve to illustrate its rarity.

- Within 3 months after vaccination there were 8 cases.
- Within 6 months and over 3 months there were 6 cases.
- Within 12 months and over 6 months there were 6 cases.
- Within 18 months and over 12 months there were 2 cases.
- Within 24 months and over 18 months there were 2 cases.
- Interval unknown 3 cases.

HARVEY SOCIETY

TABLE XI.

Case	Date	Patient	Interval	Station
1	Aug. 2, 1909	R. J.	6 days after second dose	Transport.
2	Mar. 6, 1910	A. T.	9 months after second dose	P. I.
3	June 7, 1910	A. S.	1 month after third dose	Fort Mott, N. J.
4	July 24, 1910	R. J. S.	4½ months after third dose	P. I.
5	Aug. 5, 1910	E. L.	3½ months after third dose	Ft. Benj. Harrison, Ind.
6	Aug. 5, 1910	B. F. H.	1 month after third dose	Ft. Washington, Md.
7	Aug. 7, 1910	S. P.	1 month after third dose	Ft. Washington, Md.
8	Dec. 20, 1910	H. D. C.	4 months after third dose	P. I.
9	Jan. 12, 1911	J. B.	9 months after third dose	?
10	May 12, 1911	R. K.	5 days after third dose	Point Loma, Calif.*
11	May 9, 1911	J. D.	21 days after third dose	San Antonio, Texas.
12	June 12, 1911	R. C. K.	Point Loma, Calif.
13	July 10, 1911	G. M.	San Antonio, Texas.
14	Sept. 25, 1911	F. H. S.	3 months after third dose	Ft. Sam Houston, Texas.
15	Oct. 13, 1911	H. K. M.	6½ months after second dose	Ft. Sam Houston, Texas.
16	Oct. 13, 1911	E. W.	Ft. Sam Houston, Texas.
17	June 1, 1911	A. P. B.	7 months after third dose	Japan.
18	Nov. 26, 1911	F. J. T.	20 months after third dose	P. I.
19	Dec. 28, 1911	J. C.	6 months after third dose	Porto Rico.
20	Jan. 28, 1912	W. C. E.	21 days after third dose	Ft. Slocum, N. Y.
21	June 4, 1912	J. G. K.	4 months after third dose	Field, California.
22	Aug. 3, 1912	H. S. D.	12 months after third dose	Ft. Williams, Me.
23	Aug. 30, 1912	W. M. C.	17 months after third dose	Ft. Oglethorpe, Ga.
24	Oct. 15, 1912	A. E. S.	21 months after third dose	Ft. Leavenworth, Kan.
25	Oct. 18, 1912	A. J. B.	13 months after third dose	Washington, D. C.
26	Apr. 15, 1912	F. F. T.	4 months after third dose	Schofield Barracks, H. T.
27	Aug. 16, 1912	M. C. (P. S.)	8½ months after third dose	P. I.

* History of typhoid in 1905.

It is evidently impossible from this small collection of cases occurring in our service to draw any conclusions as to the duration of the immunity.

The experience of the English Army in India, shows ³⁶ that the immunity begins to fall off after two and a half years. This, however, does not assist us greatly since the difference in the preparation of the vaccine and our use of three doses to the English two, leads us to hope for a greater degree and longer duration of the immunity.

That there is some justification for this expectation, can be shown by comparing the results obtained among English troops in India, in 1911,³⁷ with those obtained in the entire American Army, at home and abroad for the same year.

TABLE XII.
TYPHOID FEVER, 1911.

	Total strength	Absolute numbers		In vaccinated persons	
		Cases	Deaths	Cases	Deaths
English troops in India .	72,371	170	22	106	11
Entire American Army .	82,802	70	8	11	1
Ratios					
	Admissions per 1000	Deaths per 1000	Case mortality		
India	2.3	0.3	12.9 per cent		
U. S. and colonies . .	0.85	0.1	11.4 per cent		

In considering this table one should, of course, remember that typhoid is a much more common disease in India than in either the United States or its colonies and the chances of infection are therefore greater. Vaccination has also been used in India since 1904; and it is possible that the interval between

³⁶ Firth: Journal Royal Army Medical Corps, 1911, xvi, 589.

³⁷ Report, Health of Army for 1911, Lond., 1912, liii, 37.

vaccination and infection may, in some cases, have been a long one. It is probable, nevertheless, that our agar vaccine, and the use of three doses rather than two, are the main factors in producing better results in our service.

The old idea that the protective power of the vaccine lasted only so long as agglutinins and other antibodies were demonstrable in the serum, has been largely discredited; since we know that agglutinins, at least, are present in the serum of vaccinated persons for at least as long as they are demonstrable in persons who have had typhoid, who are, as a rule, immune for life.

Further essentials of a good vaccine are that it be available in ample quantity at short notice; that it be stable enough to be stored for at least three months, and to be shipped about the country for use by any physician. These requirements rule out the greater number of the vaccines proposed. It is possible, in fact, probable, that the future will give us better vaccines than we now use, yet no vaccine can be seriously considered, which does not fulfill these conditions.

The principal modifications suggested in late years are those of Vincent, of the French Army and Metchnikoff and Besredka.

Vincent's⁸⁸ vaccine is made as follows: several strains isolated in the neighborhood in which the vaccine is to be used, are grown on agar 24 to 48 hours; the growth is taken up in salt solution and kept at 37° C. from 2 to 4 days; after centrifugation, the supernatant fluid is sterilized by being shaken with ether, which is then allowed to evaporate. Three or four injections are given at short intervals.

Vincent reports the following results from Algeria:

2,632 Not vaccinated	171 cases	64 per 1000
129 Vaccine of Wright	1 case	7 per 1000
81 Vaccine bacillary polyvalent	0 cases	0 per 1000
73 Autolysate polyvalent	0 cases	0 per 1000

⁸⁸ Compt. Rend. de l'Acad. Sc., 1910, February 7, and 21; Compt. Rend. de la Soc. de Biol., 1911, July 29; Bull. de l'Acad. de Med., 1910, 40, 226; Bull. de l'Acad. de Med., 1911, 4, 63.

These and other results so far reported by Vincent are excellent and, thanks to his work, opposition is rapidly disappearing in France and vaccination is now being used to some extent in the Army and Navy. We have had no personal experience with it.

Metchnikoff and Besredka ³⁹ have conducted the most extensive investigation of recent years, using chimpanzees as test animals. They found, in these animals, that killed vaccines were powerless to prevent typhoid fever when overwhelming doses of infectious material were used, but that prophylactic immunization with sensitized living bacilli gave these animals power to resist even large doses, such as may occur in milk-borne epidemics. Interesting and valuable as this work of Metchnikoff and Besredka undoubtedly is, it nevertheless deals with a limited number of apes, and for practical purposes cannot, I think, be compared to our work with nearly 200,000 human beings.

If you will again glance at Figs. 1 and 2 and Tables VI, VII and VIII, it will be evident that our present vaccine is conferring immunity in as great a degree as has ever been done by any vaccine. It is certain that in our service typhoid prophylaxis is quite as successful as vaccination against smallpox, our old ideal of what a prophylactic measure should accomplish. It is evident from this that the opinion held by many scientists, that living vaccines and viruses are superior to dead vaccines, and that a high degree of immunity can only be conferred by the use of living vaccines, must be reconsidered, at least so far as typhoid fever and smallpox are concerned; our experience has definitely demonstrated that the immunity conferred by dead typhoid bacilli is in no way inferior to the immunity against smallpox conferred by living vaccine virus.

Excellent as the living, sensitized vaccine of Metchnikoff undoubtedly is, there are at the present time, certain insuperable objections to its use in our service; it consists of living bacteria and is not stable and cannot be stored even for short periods. Although it appears to be safe to inject attenuated

³⁹ Ann. de l'Inst. Pasteur, 1911, xxv, 193.

vaccines subcutaneously, there is still a question, if they could be handled safely, and might not accidentally infect persons by the mouth. Another objection is the possibility of contamination. This is not theoretical as it has occurred twice in the history of cholera vaccination with disastrous effects upon the progress of the movement. Contamination of a killed vaccine can be absolutely ruled out at the time of its preparation, and enough antiseptic can be added without damage, to prevent further accidental contamination. Living vaccines can never be made and handled with the same confidence, and this circumstance remains a serious objection to the use of such vaccines on a large scale.

There is another point of equal if not greater importance. We, in the Army and Navy, have come to rely upon universal compulsory vaccination. Does any one imagine that the time is ripe for any physician to recommend, or for cabinet members to order, every man in the services to submit to vaccination with living typhoid bacilli? From a few conversations with persons in authority, the idea has been firmly impressed upon me that the time for that has not yet arrived.

Would it be possible to achieve the same good results by voluntary vaccination with a living vaccine of equal protective power? How many would volunteer for vaccination under such circumstances? Certainly no more than at present. In the English Army in India, after eight years of success and hard work, 85 per cent of the men are vaccinated, and it seems improbable that this percentage can be appreciably increased. We have learned by experience that typhoid searches out and often finds the unvaccinated man. Twelve out of eighteen cases in 1912, and thirty-seven out of forty-four in 1911, were among the very small uninoculated portion of our Army. It seems, therefore, probable that greater good will be accomplished by the compulsory use of an admittedly safe vaccine, than by the voluntary use of a living prophylactic.

Our experience since 1909 has left no doubt about the success of antityphoid vaccination in the Army and Navy. The measure has come to stay. Is it not, however, desirable under

other circumstances as well? On certain points there is a pretty general agreement. Most physicians believe that the personnel of hospitals and dispensaries should be protected, since experience has shown an unduly high rate among internes, nurses, and attendants. Hachtel and Stoner⁴⁰ state that in six Baltimore hospitals the incidence among nurses and attendants over a period of five years was 12 to 20 times greater than the rate for the city. Joslin and Overlander⁴¹ found the rate among nurses in Boston was 161 per 10,000 of population as compared with twenty for the state of Massachusetts, or eight times as high.

We should, however, go a little further than this and vaccinate all who in any way come in contact with the sick, including the family and servants in contact with typhoid fever cases.

There are many other groups of persons to be vaccinated about which there is no dispute, such as those who live in industrial villages, mining towns, and isolated and temporary asylums, and especially schools.

In lumber camps, the camps of engineers, contractors and pleasure seekers, the use of the typhoid prophylactic will richly repay the time and trouble necessary for its administration.

Its use, however, is not limited to these classes of persons. The typhoid death rates for New York, Boston, Chicago, and most other large cities in the North are low, ranging from 4.7, in Bridgeport, to 17.5, in Philadelphia, in 1910, and so long as the inhabitants of these cities remain at home they run little danger of contracting the disease. Remaining at home, however, is a thing most of us do not do; we send our patients, families and go ourselves, to the country, seaside and mountains, where the typhoid rate may be many times as high as at home. Such terms as vacation typhoid, travel typhoid, are common expressions and show the danger to which we are constantly exposed. A technical term of importance in this connection is residual typhoid; *i.e.*, the typhoid which remains in a community after pure water and good sewerage have been introduced. This is

⁴⁰ Am. Jour. Pub. Health, ii, 157.

⁴¹ Bost. Med. and Surg. Jour., 1907, clvii, 247.

the typhoid we have been fighting in Army posts the past few years; it is the typhoid which remains in New York, Washington, and Richmond after these cities have been furnished with pure water. It is due to many factories, milk, flies, contaminated foods, contact with chronic and temporary carriers and with typhoid cases. Shall nothing be done to reduce the typhoid fever which remains after pure sanitation has done its best? We know from Army experience that vaccination will reduce it, surely and without danger.

Leaving the subject of residual typhoid in sanitary areas, let us consider the chances of infection in unsanitary regions, either urban or country. Here we know the chances of infection are much greater; we all know how common typhoid is in this country every summer and autumn. Osler says, "from 1900 to 1909 the death rate in the registration areas was 29.5 per 100,000. It is estimated that from 35,000 to 40,000 persons die of it every year, so that at a moderate estimate nearly one-half million people are attacked annually. It is more prevalent in country districts than in cities, and, as Fulton has shown, the propagation is largely from the country to the town."

The last census bulletin covers the year 1910, and it shows considerable improvement, the death rate being 23.5 per 100,000. It is only in half a dozen eastern cities that our typhoid rates approach the low rates of the leading cities of Western Europe, so that we have still much to do, before the typhoid situation is at all satisfactory. Each year shows some improvement, as one community after another wakes up to the fact that investments in sanitation pay better interest than gold mines; nevertheless, improvements come at a snail's pace, and many generations must elapse before this country can equal England and North Germany in its freedom from typhoid. It is admitted that sanitary administration in this country has no organization; there is no national authority with power to compel obedience; even the States show no uniformity in their powers or standards. In this matter of sanitary administration, we see the doctrine of home rule carried to the limit of absurdity. What can be done to protect against typhoid until such time as the Nation, the State and our own communities shall give proper

attention to sanitary problems, and guarantee to all, that inalienable right, the pursuit of health and happiness, free from the dangers of preventable disease? To illustrate our present dangers, one example will serve as well as another. Lumsden⁴² has reported an outbreak of gastro-enteritis and typhoid among the passengers of a Mississippi river steamer. On July 29, 1912, about 1500 persons went on a Sunday school excursion. The day was warm, the steamer's water tanks small, and to supply the demand, must often have been refilled from the river. Within a short time no less than 600 became ill of gastro-enteritis, and thirteen cases of typhoid, with three deaths, were traced by Lumsden. As the disease was not reportable in either Iowa or Illinois, where this occurred, he felt certain that all had not been recorded.

This may serve to remind us that, at the present time, sanitation alone, is not ample protection and that some measure of personal prophylaxis is absolutely essential, the moment we leave home. We are then reduced to measures of personal hygiene and individual prophylaxis, and the best method at the present time is vaccination. Only by it can we protect ourselves against infection with as great certainty as against smallpox; in this day and generation it is, in fact, the one promising method of protection from the sporadic and residual typhoid which has so far resisted the efforts of sanitarians. There is no occasion for conflict between the advocates of general and individual prophylaxis; one is as necessary as the other, and no one interested in the suppression of this disease can afford to ignore either.

All sound thinking people look forward to the time when national, state and local health authorities will unite in a concerted movement for better sanitary conditions; unite in the fight against infectious disease; when they will advance together along broad lines in the suppression of this scourge of civilization. In this campaign, antityphoid vaccination, as well as sanitation, can, I feel sure, be counted upon to play a leading rôle.

⁴² Pub. Health Reports, Washington, 1912, xxvii, 1960.

NEPHRITIC HYPERTENSION—CLINICAL AND EXPERIMENTAL STUDIES *

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WHEN Richard Bright¹ in 1836 published his "Cases and Observations Illustrative of Renal Disease Accompanied with the Secretion of Albuminous Urine," he set in motion an inquiry that has been unrestingly pursued during the past three-quarters of a century, and that is to-day still far from its goal. This inquiry concerns the phenomenon of high arterial pressure in man and its relation to chronic disease of the kidneys. In this now famous paper, Bright gave the results of his clinical study of one hundred patients, compared with the findings at autopsy. His study revealed a coincidence of cardiac and renal disease so striking as to convince him that disease of the heart must be regarded as the result, more or less direct, of the disease of the kidneys. He comments upon the relationship in these words:

"The deviations from health in the heart are well worthy of observation: they have been so frequent, as to shew a most important and intimate connection with the disease of which we are treating; while at the same time there have been twenty-seven cases in which no disease could be detected; and six others, which, from not having been noted, lead to the belief that no important deviation from the normal state existed. The obvious structural changes in the heart have consisted chiefly of hypertrophy, with or without valvular disease: and, what is most striking, out of fifty-two cases of hypertrophy, no valvular disease whatsoever could be detected in thirty-four: This naturally leads us to look for some less local cause, for the unusual efforts to which the heart has been impelled:

* Delivered February 15, 1913.

and the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately; or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

I ask you to note particularly two things. First, while Bright was convinced that he had discovered a real relationship between pathological processes in distant organs, he made no attempt to blink the fact that this relationship is by no means a constant one. Second, he did not speculate beyond certain broad inferences which, to his sane and clinically trained mind, seemed warranted by the facts themselves. These inferences were: that the hypertrophy of the heart must be attributed to unusual work performed by that organ, and that the cause of the unusual work must lie either in unwonted, direct stimulation of the heart, or in heightened peripheral resistance. Either condition, it seemed to him, could be attributed to an altered quality of the blood, associated with the disease in the kidneys. That these suggestions contained the germ of such subsequent explanations of the phenomena as have attained to any wide acceptance, bears witness to the insight into disease processes which may be gained by the attentive study of clinical symptoms in connection with the concomitant anatomical lesions. It is an insight which in the history of medicine has usually recognized its own limitations. The contrast between such modes of thought and some of the more recent speculations on the same subject is apparent.

I. THEORIES AND EXPERIMENTS

For fifty years after Bright, the origin of the cardiac hypertrophy found in kidney disease was a favorite theme of pathologists. It was the subject of extensive anatomical investigations and considerable experimental study. With the invention of the first clinical instrument for measuring blood pressure, by von Basch in 1876, the way was opened for fuller investigation of the physiology of the circulatory disorder of which the

pathologist saw the end result. Since reasonably accurate instruments were brought forward in 1896 by Riva-Rocci and by Hill and Barnard, and the sphygmomanometer has been generally adopted in medical practice, the point of attack on the problem has shifted, so that at the centre of our inquiries to-day stands nephritic hypertension.

These two problems of nephritis, the cause of the high blood pressure and the cause of the hypertrophied heart, must not be identified absolutely. In the main, however, the hypertrophied heart may be looked upon as the result of a persistently high blood pressure. To this point of view practically all authorities are now committed. The evidence for this statement is well formulated by Krehl² and by Jores.³ Such ideas as those of von Bühl,⁴ that the hypertrophy is dependent upon inflammatory processes in the heart itself, have never had wide acceptance. Even Senator,⁵ who in 1902 laid some stress on the first suggestion of Bright, namely, primary stimulation of the heart, as a factor at least in the hypertrophy found in so-called chronic parenchymatous nephritis, did not recur to this point of view in his last review of the subject.⁶ Schlayer⁷ has reported a few instances in which cardiac hypertrophy apparently preceded a rise in pressure. I, too, have seen young people in whom the heart seemed enlarged, while the blood pressure remained within normal limits. In the normal animal, with intact vagus and vasomotor mechanisms, a long maintained high blood pressure is prevented automatically. It is also a common clinical observation that high arterial pressure persists even in patients with markedly incompetent hearts, the condition called by Sahli "Hochdruckstauung." I⁸ have always been convinced, therefore, that the hypertrophy of the heart cannot explain the high blood pressure of nephritis, although it may be one contributing element. Krehl,⁹ in the last edition of his book, also insists on this. Hence, I shall confine the present discussion of the problem to nephritic hypertension, using the word "nephritic" for the sake of brevity, not in any strict sense, but to indicate only association with disease of the kidneys. Until pathologists can all agree upon the diseases of the kidney which they will con-

sider inflammatory and entitled to the designation "nephritis," clinicians may be pardoned for saving the time of their audiences by a loose use of terms.

While I shall present mainly the results of the newer clinical and experimental studies upon the subject, due weight must be given to the mass of anatomical evidence as to the relative frequency of cardiac hypertrophy in the various types of nephritis. A theory of nephritic hypertension must be adequate to explain the underlying anatomical facts, as well as the varied behavior of the blood pressure during life, including its response to therapeutic measures. It must be in accord with the recognized physiological laws governing the circulation. The problem, however, is set by the clinical facts; and it should be borne in mind that permanent hypertension is a human pathological phenomenon, which has no counterpart in the realm of normal animal physiology thus far investigated.

Mechanical Theories.—The only theory which has sought to explain the hypertension of nephritis on different lines from those suggested by Bright has been the pure mechanical theory first advocated by Traube,¹⁰ and elaborated by Cohnheim.¹¹ In its original form it sought to explain high pressure by increased peripheral resistance in the kidney itself. This theory was disproved by the observation that ligation of both renal arteries fails to raise the blood pressure. It has recently been resurrected in modified form by Katzenstein,¹² who claimed to get a slight rise in blood pressure after incomplete occlusion of the renal vessels and after temporary complete occlusion, by which he claimed to produce thrombosis of the smaller renal arteries. There was a rise in the blood pressure of the animal when the circulation was re-established. Further experiments in this direction, made by Müller and Maas,* who embolized the kidney extensively with paraffin, failed to demonstrate a rise in blood pressure. Alwens,¹³ also, does not confirm Katzenstein's observations; but he was able to produce small rises in blood pressure by compressing the kidneys in oncometers, using an amount of external pressure approximating or surpassing

* Quoted by Senator.*

the aortic blood pressure. The same amount of pressure applied to the lower extremities was without influence. Alwens himself admits that the rise in pressure obtained under these conditions is too slight, as compared with the hypertension of nephritis, to suggest that the mechanical factor is more than subordinate in the production of human high blood pressure. He admits also that the mechanism is purely passive, the actual transmission of the pressure exerted upon the kidney out through the renal artery to the aortic blood column. Such a procedure, as Senator⁶ remarks, can have no counterpart in human pathology, where the only source of pressure available is the existing aortic blood pressure.

A theory which can in part be interpreted as mechanical was propounded by Loeb¹⁴ from Krehl's clinic. It was based upon the claim that the anatomical study of nephritis showing hypertension brought out a parallelism between the extent of glomerular changes and the height of the blood pressure. Upon this finding was based the theory that the hypertension of nephritis should be considered in the nature of a regulatory function, probably evoked reflexly, in order to provide an adequate flow of blood through the kidney, when local vasodilatation within that organ was no longer sufficient, because of capillary obliteration in the diseased glomeruli. The anatomic basis of Loeb's theory has been destroyed by Jores,⁸ in a careful study of serial sections taken from the kidneys of four subjects. The two who had shown the highest blood pressure and the most marked cardiac hypertrophy, had the least extensive glomerular lesions. He also cited one instance where the heart was markedly hypertrophied and the kidneys showed scarcely recognizable histological changes. Certainly no one who has had the opportunity to observe a large series of autopsies on nephritic individuals can fail to agree with Jores, that there is no strict parallelism between glomerular changes and blood pressure. While it seems clear that the types of nephritis most regularly characterized by hypertension are characterized equally by extensive glomerular lesions, it is also evident that there exists, as Bright observed and as all subsequent statistics have shown, many instances of extreme glomerular nephritis without cardiac

hypertrophy.* The most fatal objection to a purely glomerular theory of hypertension lies in the fact that amyloid disease, which is *par excellence* a disease of the glomeruli, in its pure form is almost invariably without effect on the blood pressure, and without an accompanying hypertrophy of the heart. This fact is one of the most difficult to be reconciled with any theory of nephritic hypertension.

Chemical Theories.—The germ of the many chemical theories, as we have seen, lies in Bright's suggestion that altered composition of the blood is the probable cause. Johnson¹⁹ first elaborated this suggestion into the conception that accumulated waste products, due to failure of the excretory function of the kidney, cause vasoconstriction and later hypertrophy of the muscular coats of the arteries. The older experimental work along this line gave inconclusive results. Excision of a single kidney was without clear-cut effects, and double nephrectomy led to too rapid death for cardiac hypertrophy to develop. Recent experiments by Mosler,²⁰ in which thirteen rabbits survived the removal of both kidneys for forty-eight hours, showed a rise in the carotid blood pressure of all the animals but two, the rise being over 15 millimeters in four, and 25 millimeters in one. Real insight into the problem of the complex changes accompanying quantitative renal insufficiency was first afforded by the admirable studies of Tuffier,²¹ and especially of Rose Bradford.²² The latter excised one kidney in a large series of dogs, and watched the effect of removing successive portions of the remaining kidney. Bradford discovered that the removal of three-fourths of the total kidney substance resulted in death by emaciation and asthenia in from one to six weeks. The removal of two-thirds often resulted similarly;

* Von Bühl,¹⁸ extremely contracted kidneys without enlargement of the left ventricle, 7.9 per cent.; Potter,¹⁹ 66 cases of chronic interstitial nephritis, no hypertrophy 58 per cent. (a large number of these were in aged or greatly debilitated individuals, and the estimate of hypertrophy was not by Müller's method of weighing); von Bamberger,²⁰ 807 cases of primary Bright's disease, enlargement of the heart in 344, or 42.6 per cent.; Hirsch,²¹ weighing by Müller's method small amount of material, 72 per cent.

but if less than two-thirds was taken out, the animal showed practically no serious disturbances. His findings have been corroborated by Pearce²³ and his co-workers, who have improved upon the methods and have made valuable studies of nitrogen metabolism in such animals. Pearce occasionally was able to remove even three-quarters of the kidney substance in dogs, without producing serious symptoms. It is clear, then, that for dogs the "factor of safety" in the kidney, in Meltzer's²⁴ sense, is approximately two-thirds; and the indispensable amount of kidney substance required by the animals is not over one-third. Animals with these extreme reductions in kidney substance, which may be considered analogous to advanced kidney atrophy in man, developed early and marked polyuria.

In 1905, Pässler and Heineke²⁵ applied this method to the problem of hypertension. They argued that, as high blood pressure is most common in individuals with contracted kidneys, it was reasonable to suppose that some relation between blood pressure and amount of functioning kidney tissue would be disclosed. They performed successive reductions of kidney substance in eighteen dogs, of which seven lived longer than four weeks without severe cachexia. On five of these dogs they made satisfactory blood pressure observations, by taking readings from the femoral artery before operation, eight days after operation, and several weeks after the last operation. These dogs showed an average increase in the blood pressure of 21.5 millimeters, the maximum increase being 29, and the minimum 15 millimeters. If too much tissue was removed, a cachectic state ensued and the blood pressure fell. These five dogs also showed well-marked hypertrophy of the left ventricle as compared with the right. For all seven the average proportionate weight of the left ventricle to the right showed an increase over the normal of 28.5 per cent. These dogs quite regularly developed polyuria before the rise in blood pressure occurred. No reasonable criticism can be urged against these experiments. Pässler,²⁶ in a review of the whole subject, based on his experiments and clinical studies, concludes (1) that the hypertrophied heart in nephritis is the consequence of the kidney disease; (2) that as a

result of the kidney lesion there probably occurs an increased irritability of the vasoconstrictor apparatus, in consequence of which arise arterial spasm and increase of resistance in the aortic circulation; (3) that the hypertrophy of the left auricle and of the right heart in nephritis is a later consequence of insufficiency of the left ventricle. This he argues not only from the finding of pure left ventricular hypertrophy in his experiments, but from a critical review of the clinical evidence, which seems to me satisfying.

Formerly, hypertrophy of the entire heart, right as well as left, frequently found in the extensive *post-mortem* statistics, seemed a serious obstacle to the acceptance of any theory which sought to explain the hypertrophy on the basis of increased resistance in the aortic circulation. Krehl, in the earlier editions of his "Pathologische Physiologie," was strongly impressed with the difficulty of explaining this right ventricular hypertrophy. Many attempts were made to discover factors which would influence equally the right and the left heart. Increased viscosity of the blood, for instance, was postulated until clinical studies showed that this did not usually exist in hypertensive nephritis.²⁷ There is a small but interesting group of patients in whom polycythaemia and chronic hypertension are associated, the so-called *polycythaemia hypertonica* of Geisböck.²⁸ These cases differ from ordinary polycythaemia in the absence of an enlarged spleen. That increased viscosity in itself cannot explain hypertension is clear, however, from such an example as that reported by Lommel.²⁹ In his patient extreme polycythaemia was unassociated with rise in blood pressure during life or hypertrophy of the heart at autopsy. Lucas³⁰ has recently reviewed 189 cases of erythroæmia, and finds that hypertension existed in only a third.

Changes in the right heart are most often lacking in young persons dying accidentally, or without a long illness. I have seen exquisite concentric hypertrophy of the left ventricle alone in a girl of sixteen, with extremely contracted kidneys, who died in uræmic convulsions. The weighings of Hirsch,³¹ by Müller's method, have shown that the usual sequence of events

is: first, hypertrophy of the left ventricle, later in the disease the development of disturbances of compensation, then consecutive hypertrophy of the right ventricle. That another factor may perhaps be involved is suggested by Stewart's²² study of cardiac hypertrophy resulting from the artificial production of aortic insufficiency in dogs, a purely mechanical lesion. All the chambers of the heart in his animals showed some increase in weight, though the increase was by far the greatest for the left ventricle.

In 1908-1909, with the assistance of Carrel, I attempted to study more in detail the increase in blood pressure following reduction of kidney substance.²³ As it is not possible to take innumerable blood pressure readings directly from an artery, I devised a modified Riva-Rocci method,²⁴ by means of which I was enabled to take approximate readings from the foreleg of the dog. The blood pressure was studied in twenty-three dogs. On ten, an operation for the excision of one kidney was made, with infarction of a considerable portion of the remaining kidney by ligature of branches of the renal artery at the hilum. Some of the animals were lost because of too extreme reduction of kidney substance, and from accidental causes. One dog (No. 19) survived the operation thirty-nine days; he did well for twenty-one days, but then went into a state of progressive cachexia with gastro-intestinal disturbances, as described by Bradford²² and by Pearce.²³ The blood pressure, which had averaged 106 millimeters before operation, and 127 millimeters during the first twenty-one days, fell to an average of 83 during the terminal illness.

Blood Pressure Readings in Millimeters on Dog No. 19.

	Maximum	Minimum	Average
Before operation, 15 days, 4 readings..	110	100	106
After operation, 21 days, 7 readings..	135	120	127
Terminal period, 14 days, 3 readings..	110	70	83

The above is analogous to what one sees occasionally when human beings with high pressure develop a terminal infection or wasting disease. Two dogs showed unequivocal, sustained

hypertension; they were followed for 104 and 163 days respectively. Polyuria was evident, as in former experiments of this type. Albumin was usually present in the urine, which Pearce³⁵ has suggested evidenced nephritis in the remaining functioning kidney; but except in the neighborhood of the infarct, the histological appearances were normal.

Blood Pressure Readings in Millimeters on Dog No. 12.

		Maximum	Minimum	Average
Before operation, 45 days, 7 readings..		110	80	90
After operation, reduction of circulation				
to one kidney,				
First 28 days, 8 readings.....		120	100	111
Second 28 days, 10 readings.....		140	110	119
Third 28 days, 11 readings.....		150	110	121
Fourth 28 days, 12 readings.....		140	110	126
Fifth 28 days, 7 readings.....		130	115	120
Sixth 23 days, 7 readings.....		145	120	134

Blood Pressure Readings in Millimeters on Dog No. 20.

		Maxi- mum	Min- imum	Average
Before operation, 23 days, 11 readings		135	95	117
After operation, first 28 days, 13 readings		175	130	157
After operation, second 28 days, 15 readings		165	130	150
After operation, third 28 days, 6 readings		185	150	158
After operation, fourth 20 days, 6 readings		165	150	156

These experiments, it seems to me, confirm and extend the results obtained by Pässler and Heineke.²⁵ They have not the same validity as a demonstration of the effect of purely quantitative reduction of kidney substance, as the infarcted portion of kidney was left *in situ*. It might be urged that the high blood pressure was the result of absorption of the products of disintegration of kidney tissue in the infarcted area; but the duration of the high blood pressure for weeks after the infarct was converted into a mass of partly calcified fibrous tissue, would seem to make this criticism negligible.

From the standpoint of the dog, therefore, it seems clear, as Pässler and Heineke have shown, that moderate hypertension follows the quantitative reduction of kidney tissue to about a

third of the total. My experiments show that such hypertension may be maintained for a long period. The rise in blood pressure thus produced is, therefore, more analogous to the hypertension of chronic nephritis in man than the transient hypertension of most animal experiments dealing with this problem. By what mechanism this increased blood pressure is brought about, is wholly obscure; but that it must be associated, as Pässler²⁶ predicates, with increased tonus of the systemic arteries, seems inescapable.

Renin.—Many attempts have been made to discover chemical substances exerting a pressor effect which could be conceived as accumulating in the blood in kidney disease. Simple retention of urea or other metabolites failed to accord with the facts. In 1898, Tigerstedt and Bergman²⁶ extracted from the rabbit's kidney a substance which they called renin and which, when injected into animals, produced a rise of blood pressure. H. Batty Shaw²⁷ reviewed this subject extensively in the Goulstonian lectures for 1906 and advocated with enthusiasm the theory of autolysis of the kidney, with liberation of some pressor substance of this type, as the explanation of nephritic hypertension. Bingel and Strauss²⁸ have confirmed the pressor effects of renin. More recently, Pearce²⁹ has investigated the effects of kidney extracts from various animals on the same and other animal species, with altogether variable results. For instance, the extract of dog kidney injected into the dog caused a decided fall in blood pressure; the same was true of rabbit's extract; while rabbit kidney and dog kidney extracts injected into the rabbit produced a slight rise. J. L. and E. M. Miller⁴⁰ have failed to obtain pressor effects from saline extracts of kidney or of any other organ except the spleen, hypophysis, and adrenal. It is, moreover, an acknowledged clinical fact that hypertension is most extreme in those exquisitely chronic types of nephritis in which the breaking down of kidney substance must be at a minimum, if there is any at all. This fact, to my mind, so argues against the hypotheses that have been cited, that I think it is reasonable to dismiss them from consideration.

Epinephrin.—The search for a chemical principle within the body by which to explain the phenomenon of increased blood pressure seemed to have attained its goal in Oliver and Schäfer's⁴¹ discovery of the remarkable effects produced by extracts of the suprarenal gland. The development of the adrenalinæmia theory of hypertension makes a fascinating chapter in the history of speculative medicine. It is so rich in lessons, and belief in the theory is so widespread, that I propose to sketch it in detail. The hypothesis that increased secretion of the suprarenals might be the long-sought cause of nephritic hypertension was first proposed by Neusser,* but merely as a shrewd guess, from a single clinical case of chronic Bright's disease with carcinoma of one adrenal. The first attempts to bring forward arguments in support of the assumption were made in France. Vaquez⁴³ in 1904, in a paper before the French Congress of Medicine, produced some autopsy observations made by his pupils, Aubertin and Ambard, showing the presence of nodular hyperplasia of the suprarenals, and of actual adenomata, in cases of hypertensive nephritis; and brought into line with them, Josue's recent studies of the arterial lesions produced by epinephrin. This evidence was received with enthusiasm; but further anatomical investigations, particularly those of Landau,⁴⁴ Pearce,⁴⁵ Thomas,⁴⁶ and Borberg,⁴⁷ made on extensive material, have failed to show a constant relation between anatomical lesions of the adrenals and the hypertension of nephritis or arteriosclerosis. Similar suprarenal lesions have also been found in persons dying of other diseases. To a large extent it now seems probable that the changes found in the gland are the result of local arteriosclerosis of its own vessels, rather than *vice versa*. The experimental lesions produced by epinephrin, moreover, are quite unlike human arteriosclerosis. Pearce⁴⁵ suggests that hyperplasia of the adrenal probably represents the effect of some factor operating in the later period of life, during which chronic nephritis and arterial affections are most frequent. The relations are evidently complicated and the anatomical evidence of excessive suprarenal function is unconvincing. Perhaps the most extensive work upon

* Quoted by Biedl.⁴⁸

the subject is Ingier and Schmorl's⁴⁸ determination of the epinephrin content of the adrenals in 517 autopsies. They found an increase of epinephrin in the glands in acute nephritis, and in seventeen patients with chronic nephritis, with higher values on the average in those having high blood pressure and hypertrophied hearts. On the other hand, their highest figure—almost three times the normal average—was from an individual without either an hypertrophied heart or arteriosclerosis; and the three next highest figures were from similar cases. Again, the subject with the greatest cardiac hypertrophy showed a far lower epinephrin content—actually less than the normal. These results can be more readily explained along the lines suggested by Pearce.⁴⁹

The well-marked hypotension of Addison's disease, and the rapid death with a sharp fall in blood pressure which followed the earlier extirpations of the adrenals, were assumed to be the reverse side of the picture. To many minds the evidence of diminished adrenal secretion seemed so clear that the assumption of increased adrenal secretion as the cause of the opposite effect upon blood pressure and heart was an easy step. But the more the cause of death after removal of the adrenals has been studied, and the better the operative technic employed, the further have the effects upon blood pressure receded into the background. Many investigators have now succeeded in extirpating the adrenals, or in excluding them from the circulation by ligature of their veins, without producing immediate effects upon blood pressure. After Hultgren and Anderson's* technically perfect removal of the adrenals, the blood pressure in some of the animals remained normal for two or three days. In this country, Hoskins and McClure⁵⁰ have recently performed similar experiments. They seem to me of crucial importance. The effect of epinephrin is so very transient that, were the normal tonus of the blood-vessels dependent upon its presence, the exclusion of the suprarenals from the circulation must cause a prompt and unmistakable fall in blood pressure. Furthermore, there seems reason to believe that the cortex, not the medulla of the adrenal, is the structure essential to life.

* Quoted by Biedl.⁵¹

The cortex, as is well known, plays no part in the elaboration of epinephrin. The whole question is extensively discussed by Biedl⁵¹ and by Bayer;⁵² Biedl seems to lean toward this view. Plainly, therefore, the hypotension of Addison's disease can in no wise be used as an argument to bolster up the assumption that hypertension is an affair of hypersecretion of the adrenals.

With the increasing activity of physiologists in investigating the action of epinephrin, methods became available for its identification in exceedingly dilute solutions. Batelli⁵³ reported in 1902 that he obtained a pressor effect by injecting concentrated dog serum into rabbits, which corresponded to an epinephrin concentration in the blood of 1 to 20,000,000. The first clinical work to attract widespread attention to the supposed presence of epinephrin in the circulating blood of nephritics was a publication by Schur and Wiesel.⁵⁴ Their test object was the excised eye of the frog, which dilates with epinephrin, a reaction first described by Meltzer.⁵⁵ They also claimed to identify epinephrin chemically by the ferric chloride reaction. Schur and Wiesel⁵⁶ prophesied that it would soon be proved that the high blood pressure, the cardiac hypertrophy, and the vascular changes of kidney disease are related to increased activity of the chromaffin system, which was at that time beginning to attract wide notice. Schlayer⁵⁷ promptly made tests by the Meyer artery strip method, using normal sera and, in ten experiments, nephritic sera from hypertensive patients. He found that normal serum, even after removal of the albumin, always contained a constrictor substance which resisted dialysis, was diminished by concentration *in vacuo*, and therefore resembled epinephrin. The nephritic sera, in all but one case, produced much less constriction than normal sera. He concluded, therefore, that Schur and Wiesel's results had no validity, because they had been unable to identify an epinephrinlike substance in normal blood, and held that the hypothesis of a connection between nephritic hypertension and adrenal function was as yet unproved. Schlayer⁵⁸ made a number of other studies by the Meyer method,⁵⁹ and came to the conclusion that arteries would not react to epinephrin in any but

homologous blood. Fraenkel,⁶⁰ using the uterus suspension as a test object, Trendelenburg,⁶¹ using the frog perfusion preparation of Läwen,⁶² and later, Bröking, and Trendelenburg,⁶³ all failed to get greater constrictor effects from the blood of patients having high pressure than with blood from normal persons. Kretschmer's⁶⁴ results, with the Meyer method, were positive in acute, negative in chronic nephritis. However, the extreme vasoconstriction produced by the defibrinated blood or serum, which all used, seemed to reproduce the effect of epinephrin so exactly that the presence of this in normal blood was accepted without question.

On the basis of Langley's and Elliott's⁶⁵ studies of the relation of epinephrin to the sympathetic nervous system, it began to be assumed that the maintenance of normal vascular tonus in the intact animal and man must be altogether dependent upon the constant secretion of epinephrin into the blood by the chromaffin tissue in the medulla of the suprarenal and elsewhere. The more this was taken for granted, however, the more difficult did it become to understand why an epinephrin effect was so often absent in states of high blood pressure. In October, 1911, G. N. Stewart⁶⁶ published a severe criticism of all these experiments as based upon inadequate evidence that epinephrin was the substance causing the reactions described. He called attention to the fact, which most of the clinical investigators had disregarded, that the property of stimulating the smooth muscle of artery or pregnant uterus is not peculiar to epinephrin. He suggested that, as epinephrin evokes from certain other smooth muscle preparations, the intestinal ring for instance, the opposite effect, inhibition with loss of tone, no test for it in complex body fluids should be considered positive which did not demonstrate both types of reaction in the sample examined.

The beautiful dream of adrenalinæmia, however, was not seriously disturbed until O'Connor,⁶⁷ in March, 1912, published the results of his painstaking and ingenious investigation of the subject. He proved clearly that the vasoconstrictor substance in defibrinated blood and serum, which had been mis-

taken for epinephrin, was equally stimulating to intestinal peristalsis, and was, therefore, from this standpoint the *antagonist* of epinephrin. He furthermore proved that no constrictor effect was produced by blood which was prevented from coagulating by the addition of citrate or hirudin. The supposed epinephrin of defibrinated blood serum was apparently some substance produced during the process of clotting, and not present in the circulating blood at all. Definite evidence of epinephrin in the blood he could obtain only in that from the adrenal veins.

The further researches of Stewart,⁶⁸ published within a fortnight, while confirming the absence of epinephrin reactions in peripheral blood, go to show that the whole subject is very complicated, and that the mere prevention of clotting does not always suffice to make shed blood an indifferent fluid in smooth muscle. Bloods kept from clotting by citrate, hirudin, and peptone are not identical in their effects. These studies again emphasize the need for extreme caution in interpreting the biological reactions obtained with so complex a fluid as blood, as due to any one supposed constituent.

Before the publication of O'Connor's article, Park and the writer,⁶⁹ as the result of a long series of experiments made by a modified Meyer method, had already reached the conclusion that the vasoconstrictor substance of defibrinated blood was not epinephrin. We used as our test objects rings of the carotid artery of the ox which are constricted by epinephrin, and rings of the coronary which undergo dilatation.⁷⁰ Defibrinated blood and serum produced extreme constriction of *both* preparations. The character of the curve was different from that produced by epinephrin; it was similar to that of barium chloride, a substance known to act directly upon smooth muscle, whereas the point of attack of epinephrin is the so-called "receptive" substance, the neuromuscular junction between the sympathetic nerve fibre and the smooth muscle. It was clear that the serum constrictor substance acted upon smooth muscle directly, and had no relation to its sympathetic innervation. We had made a number of unsuccessful attempts to identify low dilutions

of epinephrin in serum. After the publication of O'Connor's work, we studied normal human blood and blood from six patients having high pressure, with and without nephritis. In most of the experiments we prevented clotting of the blood by the use of hirudin, in a few by citrate. Neither in normal blood nor in the blood from hypertensive patients could any definite trace of an epinephrin effect be obtained.

O'Connor's results have also been amply confirmed by Schultz,⁷¹ who has, however, made no studies of nephritic blood. Using trustworthy methods, Cannon and his collaborators,⁷² and Hoskins and McClure,⁷³ have identified epinephrin in blood from the adrenal veins. Stewart⁷⁴ has succeeded only when the gland was disturbed or stimulated. He has failed to obtain any evidence of its existence in pathological sera.

Hoskins and McClure⁷⁵ feel confident that they have shown that the quantity of epinephrin necessary to produce a minimal rise in blood pressure is from ten to twenty times the amount secreted by the suprarenal glands per minute. As they have further shown that the injection of an amount sufficient to raise blood pressure causes a complete inhibition of intestinal peristalsis, they argue that adrenal secretion cannot be a direct factor in the maintenance of the normal tonus of the vasomotor system. They agree with O'Connor⁶⁷ in estimating the probable epinephrin concentration of general arterial and venous blood at 1 in 200,000,000, an amount undetectable by the most delicate methods.

The possible assumption remained that repeated doses of epinephrin below the minimum effective single dose might increase the tone of the vessels. Park has recently tested this for me on the artery strip. His results have been absolutely negative. Lieb has also performed a few experiments to try on the isolated vessel the supposed synergism of hypophysis extract and epinephrin, which Kepinow⁷⁶ claimed to find. He has been unable to confirm it.

The work of Cannon and his collaborators,⁷² already alluded to, showed a marked increase in epinephrin output under the influence of anger, fear, and strong sensory stimulation. The

splanchnic nerve seems to contain secretory fibres for the adrenal. Two articles by von Anrep,⁷⁶ which have just appeared, show that the normal effect of splanchnic stimulation in an intact animal is a short, primary rise in blood pressure, followed by a secondary rise, which is accompanied by increased tonus of the heart and marked peripheral vasoconstriction. Similar stimulation, after exclusion of the suprarenals by clamping the vein, results only in a moderate rise in pressure, continuous with the primary rise, with dilatation—not constriction—of the heart and the peripheral arteries. The conclusion drawn seems warranted—that the secondary effects of splanchnic stimulation are dependent upon the discharge of epinephrin into the blood stream.

Blood Sugar.—The problem has been approached from one other side, namely, by the investigation of the blood sugar. It is well known that the injection of epinephrin into an animal whose liver contains glycogen results in an increase of sugar in the blood, which, if it reaches a sufficiently high percentage, produces transient glycosuria. It has, therefore, been reasoned that if hypertension be associated with increased circulating epinephrin, hyperglycaemia should be found. Patients with high blood pressure, with and without nephritis, have, therefore, been investigated by various observers, with conflicting results.* At present, the problem is being investigated in my service at the Presbyterian Hospital, by Geyelin. The table on page 226 illustrates the most striking hyperglycæmia yet observed in chronic nephritis.

I ask you to note that the blood sugar has increased from a figure at the upper limit of normal to a marked hyperglycæmia in eleven weeks, while the blood pressure was highest at the first and lowest at the last observation. This increase, while unrelated to the height of the blood pressure, has, however,

* Neubauer,⁷⁷ especially, claims to have found marked increases in blood sugar. Hagelberg,⁷⁸ Wieland,⁷⁹ and Port⁸⁰ found significant increases only in cases with marked uræmic symptoms, eclampsia, or apoplexy. Stilling,⁸¹ Tachau,⁸² Schirokauer,⁸³ and Frank⁸⁴ have failed to find definite hyperglycæmia. The latter worked especially with so-called essential hypertension cases.

been coincident with the advance of his kidney lesion, increasing ureæmic symptoms and a rise in the urea content of the blood, indicating coincident nitrogen retention. These figures seem to me much more in accord with the theory of renal retention than of epinephrin hyperglycæmia, though one cannot in-

HYPERGLYCAEMIA IN CHRONIC NEPHRITIS.

Date.	Diet.	Blood sugar per cent	Urea per cent	Blood pressure
Nov. 25	Soft, NaCl poor	0.009	0.168	234 mm.
Dec. 20	Soft, NaCl poor	0.133	0.188	220 mm.
*Jan. 18	Glucose, 100 gm. Two hours after, glucose excreted in urine, 0.26 gm.	0.201	230 mm.
*Jan. 22	Glucose, 100 gm. Two hours after, glucose excreted in urine, 0.12 gm.	0.192	225 mm.
*Feb. 8	N. poor, 36 hours after ureæmic convulsion	0.1605	0.375	205 mm.

* Epinephrin tests made on samples taken on these days.

terpret them with any positiveness. In view of the possibility of technical errors and of retention of sugar by the diseased kidney, it is the part of wisdom to reserve opinion upon the whole question until extensive work has been done by the newer, more accurate methods. Even should hyperglycæmia prove to be frequent in such patients, it would be absurd to consider it more than suggestive of increased circulating epinephrin, as it might be dependent upon other, wholly unrelated disturbances or renal impermeability.

In addition to this investigation, Lieb and I have recently made one more attempt to identify epinephrin in the peripheral blood from a patient in whom positive results might certainly be expected, if the epinephrin theory of hypertension has any basis. The patient was the one in whom the notable hyperglycæmia was found. The blood, prevented from clotting by hirudin, was tested on January 18, 22, and February 8, on the last date thirty-six hours after a ureæmic convulsion; bleeding was done for therapeutic purposes. On the first date,

dilatation of the coronary was obtained, but of an extent comparable to that produced by not less than 1 to 10,000,000 epinephrin. At the same time, a constriction of the peripheral artery was produced, but the form of the curve was different from any which I have ever seen due to epinephrin. This blood was also tested for its effect in dilating the pupil of the rabbit's eye, after removal of the left superior cervical ganglion. Meltzer⁸⁵ has found this an extraordinarily delicate test for epinephrin. A slight increase in diameter was observed in two such eyes, the control eye and the eyes of control rabbits showing no dilatation, or slight constriction. The light conditions for this test were, however, not entirely satisfactory.

For this reason, additional tests were made on January 22. In these, the carotid response was typical of epinephrin; the coronary, however, showed a primary constriction followed, after three minutes, by a marked dilatation. This cannot be claimed as an epinephrin response, though it is possible that it may be the combination of an epinephrin effect with vasoconstriction from some other substance in the blood. The rabbit intestine test with the same blood was only faintly suggestive, in no way corresponding to the effect which might have been expected from the constriction produced in the carotid. The final test, on February 8, gave a satisfactory carotid response, but a constriction of the coronary, followed, after a still longer interval than in any other case, by dilatation, and an inhibition of the intestine so extreme and protracted as to be impossible with any concentration of epinephrin which would not have given the most typical results with the two artery preparations. These findings, while in many particulars highly suggestive of the presence of epinephrin, are entirely too variable to permit me to believe that we have identified it.*

* This patient died in uræmic coma on February 17. Autopsy revealed an extreme degree of atherosclerotic contracted kidney, and adrenals which weighed 10.37 and 8.71 grammes respectively—more than twofold the normal—with abundant medulla. Estimation of the epinephrin in half the left gland, by Folin's¹²⁰ new method, showed a content of 3.1 milligrams. The determination from the right adrenal

In order to test still further the possibility of detecting epinephrin in the blood, Lieb and I performed a final series of experiments on four dogs. These dogs were anæsthetized and control samples of blood were drawn from the right femoral artery, one into hirudin and one into citrate solution. Then a continuous infusion of epinephrin in normal saline, according to Kretschmer's method,⁸⁶ was introduced into the right femoral vein. This produced a sudden and extreme hypertension—200 millimeters or over—for at least ten minutes in the shortest experiment. Blood was taken from the left femoral artery at the end of the infusion, while the blood pressure was still high, and its action on carotid and coronary strips and the intestinal segment was compared with that of the blood drawn before the production of the epinephrin hypertension. The results of these four experiments are very disappointing. While in all we obtained positive responses with one or two of the test objects used, in no single experiment did we succeed in producing unequivocal epinephrin reactions in all three. As shown by Stewart,⁸⁸ foreign blood has at times very disturbing effects upon these living, smooth muscle preparations.

The amount of epinephrin injected for three dogs was 0.05 milligrams, and for one, 0.1 milligram per kilo. Figuring the blood volume of the dog at the minimum of five per cent., this would make the concentration of epinephrin, if the blood and epinephrin had been mixed outside the body, 1 in 1,000,000. In our last experiment, the intestinal segment showed a mere suggestion of response, whereas a perfectly distinct effect was produced by blood containing added epinephrin in concentration of 1 to 25,000,000. Such an experiment shows the extreme rapidity of the disappearance of epinephrin from the circulation. The immediate fall of pressure at the end of the

was spoiled. The gland was cut so as to divide the medulla as equally as possible. On this basis, the total epinephrin content of the two adrenals should have been 13.5 milligrams, three times Ingier and Schmorl's average figure. Histological study of the remaining halves of the glands, while showing a large medulla, failed to show a striking increase in chromaffin substance.

infusion also suggests prompt destruction or fixation of the substance, though explicable as well by Straub's⁸⁷ theory of toxic action, as illustrated by muscarin.

From these experiments I am persuaded that the attempt, by our present methods, to obtain evidences of epinephrin in the peripheral circulation is fruitless. I should go further than Stewart⁸⁸ and insist that no demonstration be considered conclusive which does not show qualitatively typical and quantitatively possible epinephrin effects, simultaneously in three different test objects, inasmuch as many confusingly similar effects may be produced by substances contained in that highly complex fluid, blood. To obtain these three reactions, as we have shown, even when epinephrin is known to be the cause of a blood pressure exceedingly high, is a matter of great technical difficulty with the biological test objects at present employed.

To recapitulate, the net result of all this labor is the solid, well-grounded fact that the suprarenal glands, or at least their medullary portions, manufacture a substance, epinephrin, which, introduced into the circulating blood, produces a rise in the systemic arterial pressure unparalleled in intensity by any other known substance. This rise is extremely transient; but the continuous, steady introduction of epinephrin is capable of maintaining a state of hypertonus as long as the introduction is continued. Accompanying this rise in blood pressure is a reduction in volume of the extremities and of many organs, due to local vasoconstriction, so that the actual blood flow through them is diminished. The coronary artery, however, is dilated by epinephrin; and intestinal peristalsis is inhibited and intestinal tonus abolished. The bronchi in a state of spasm are also relaxed by epinephrin. It is probable that during life epinephrin is constantly finding its way from the adrenals into the general circulation, but except in the blood of the adrenal veins, epinephrin has never been positively identified in the general circulation of the normal animal or man. From all the quantitative studies that have been made, as well as from other considerations, it cannot at present be assumed that epinephrin exists in the general circulation in sufficient concentration to

manifest any of its physiological actions; but during stimulation of the splanchnic nerve, either directly, reflexly, or psychically, the rate of epinephrin discharge into the circulation may be markedly increased and its action become evident. This, as Hoskins and McClure⁷⁸ suggest, should probably be regarded as a reserve mechanism of the organism to meet emergencies. Up to the present time epinephrin has not been proved to play any part in the maintenance of normal vascular tonus. There is no convincing evidence, anatomical or physiological, for any theory connecting the adrenal glands or increased circulating epinephrin with states of high blood pressure, with or without nephritis. That for some types of hypertension, or for certain acute and transient crises of hypertension, increased epinephrin discharge may in the future be demonstrated as the cause, can be neither affirmed nor denied.

II. CLINICAL FACTS

From the contentious realm of theory and experiment, I ask you to return to the more peaceful, though perhaps prosaic, domain of clinical facts. Experimental medicine has not as yet solved the riddle of hypertension; there is need for further work in that field. Nor can clinical medicine make this claim; but the facts gained by the observation of human blood pressure in disease have added greatly to our knowledge of the pathology of the circulation. They are fundamental to an adequate understanding of the theoretical problems to be solved in the laboratory and the practical problems to be dealt with at the bedside.

What do we mean by high blood pressure? That question is more easily answered to-day than it was nine years ago, because the requirement of a blood pressure reading by many life insurance companies as a part of the examination of the applicant, has made available the records of large series of normal individuals. From the compilations of Woley,⁸⁸ Fisher,⁸⁹ and Cook,⁹⁰ it is clear, as I had held previously,⁹¹ that a constant systolic blood pressure of 160 millimeters or over is pathological. It seems probable, as Cook suggests, that more extended observations will make 150 millimeters the upper normal limit.

Before middle life, pressures of over 135 millimeters are suspicious, above 145 millimeters abnormal. In Woley's series, the average for women was 7.5 millimeters lower. First readings in any person are apt to be higher than subsequent ones. When the use of the sphygmomanometer becomes as much a matter of daily routine as the taking of temperature, a still more accurate guide to pathological variations in blood pressure will be afforded by comparing the previously recorded normal pressure of the person in question. I cannot too strongly urge on practitioners the need for keeping occasional records of the arterial pressure of all patients, in order that early evidences of disease may be recognized and that our knowledge of the manner in which hypertension develops may be extended.

High blood pressure is a symptom so common that its chief manifestations are familiar to all physicians. General impressions, however, may mislead; and in order that I might present a basis of definite facts instead, I have made an analysis of the histories of 459 private patients whose systolic blood pressure registered over 165 millimeters. These records extend over a period of ten years. Upon this analysis and the survey of a selected group of hospital patients, any opinions that I may express are founded.

From a study of this kind it is clear that the patients naturally fall into certain groups as regards symptoms and clinical course. The largest group is made up of individuals well past middle life. The clinical picture which they present is usually that of some degree of cardiac insufficiency, and their death is a cardiac death. Arteriosclerosis is a commonly associated lesion; anginoid attacks are fairly frequent; about ten per cent. are elderly diabetics. While the bulk of them at some period show albumin, casts, or other urinary changes, usually interpreted as indicating nephritis, and while at autopsy the majority prove to have either arteriosclerotic atrophy of the kidneys or the so-called "primary contracted kidney," it must be borne in mind that during life many of these individuals fail to show any urinary changes other than those of chronic passive congestion. There are also a number of authenticated

autopsy cases on record, in which the same clinical picture of permanent high blood pressure has been associated with kidneys found to be normal or with only secondary congestion, due to a failing heart. I have seen such patients, and Krehl ⁹² and Schlayer ⁹³ have published records of similar ones. When these individuals consult a physician because of even minor symptoms, the blood pressure is usually found already far above normal; and although some reduction and great symptomatic improvement may occur as the result of hygienic and dietetic measures, I have only a single unequivocal record of a patient in whom the pressure returned to the normal for as long as two years. In the main, the treatment of these patients lies in safeguarding the heart. From the clinical standpoint I speak of them as cases of hypertensive cardiovascular disease.

A closely related group shows predominant cerebral symptoms—headache, vertigo, apoplectic attacks. Polyuria is found more frequently in this group, and the evidences of severe functional damage to the kidneys. Far more of them die with uræmic symptoms. The discrimination between toxic cerebral symptoms and manifestations of focal vascular lesions, or of general cerebral arteriosclerosis, is so often impossible during life that this clinical group must be considered a compound one. On the one hand it contains the older individuals whose important disease is arteriosclerosis of the brain arteries; on the other, younger persons with the so-called primary contracted kidney. A quite similar clinical picture may occasionally be presented by chronic glomerular nephritis.

Many attempts have been made to correlate the clinical picture, the functional disturbance of the kidney as revealed by the newer tests, and its anatomical lesions found at autopsy. None of these has succeeded, and at present it seems a far cry to the day when such attempts will be successful. Schlayer ⁹⁴ remarks with much reason that when we speak of chronic interstitial nephritis, we usually have in mind a definite symptom-complex, rather than an anatomical picture; and that much of the misunderstanding between pathologists and clinicians has arisen from this fact. It seems to me that we should recog-

nize clearly that the differentiation of the various anatomical types of nephritis is altogether beyond the powers of clinical diagnosis. Fortunately, it is not of very great import for us as internists, for we are practically concerned with structural changes only in so far as they give rise to disturbances of function, can be utilized for diagnosis, or afford us data for prognosis. Rarely, indeed, can we influence them directly. The kidney is a highly complex organ, and the contribution of each of its structurally differentiated parts to its total function is unknown. If correlation of structure and function is thus still impossible to the physiologist, the physician need not be ashamed of his failure to harmonize them when diseased. For the present, in the clinical study of renal disease the aim must be to achieve an exact analysis of the perverted functions and to discover the evidently remote causes, as a basis for treatment and prevention. I believe that the conception of hypertensive cardiovascular disease is justified on this physiological basis.

Where so obvious a disturbance of the circulation exists and investigation of the kidney function shows no changes of importance, it is immaterial what may be the exact appearance of the kidney; the patient must be treated from the standpoint of his circulatory disorder. The more recent pathological anatomical studies seem to justify this rather barefaced clinical point of view. In particular, the work of Jores,⁹⁵ Aschoff,⁹⁶ and Gaskell⁹⁷ shows a return of pathologists to the fundamental idea which Gull and Sutton⁹⁸ enunciated, namely, that the real disease back of what we call chronic interstitial nephritis is a disease of the small blood-vessels, and that the lesions of the kidney are secondary manifestations. Gull and Sutton may have been misled by inadequate histological methods into an erroneous interpretation of the vascular lesion, but their arterio-capillary fibrosis stood for the conception of primary vascular disease. The return to the interpretation of the primary contracted kidney as essentially a disorder of the kidney arterioles has been facilitated by Löhlein's⁹⁹ differentiation of the secondary contracted kidney, which arises out of a true glomerular nephritis, from the former confused group of atrophic kid-

neys. While there may be an overlapping of types and various combinations of lesions within the same kidney, and while it is still beyond the possibilities to agree upon either the clinical symptoms or the functional disturbances which are associated with these different types—as such studies as those of Volhard¹⁰⁰ and Frey¹⁰¹ show—there does seem to be sufficient anatomical basis for the belief that the hypertensive cardiovascular disease, which we recognize clinically, is not primarily nephritic hypertension (in the strict sense of the term), but widespread disease of the arterioles in various internal organs.⁹⁹ The disease in its fully developed form involves the kidney, producing the small, red, granular, or primary contracted kidney; but occasionally it leaves the kidney untouched. In its course, arteriosclerosis of the larger vessels may develop; hypertrophy of the heart is frequent, and death by apoplexy a common mode. On the other hand, arteriosclerosis of the larger vessels may spread peripherally, as it were, and become associated with a similar clinical picture, though less constantly leading to high blood pressure and a hypertrophied heart. This primary arteriosclerotic disease produces the patchy arteriosclerotic atrophy of the kidney, rather than the more diffuse changes of the arteriolar disease. Clinically, this form is perhaps more commonly associated with an insufficient heart. From the standpoint of physiology, the high blood pressure is the evidence of arteriolar disease, rather than renal, though it is premature to consider the relation quantitative in any sense. It must be interpreted as a sign of abnormal irritability of the constrictor mechanism. Whether it precedes the development of the anatomical lesions, as Allbutt¹⁰² and the English school have held, as Huchard¹⁰³ meant by his term "pre-sclerosis," as von Basch¹⁰⁴ taught in his conception of "angio-sclerosis," and as Jores⁸ seems to believe, cannot be regarded as settled. That it is, however, primarily dependent upon processes without the kidney seems altogether probable.

Have we any clue to the origin of this persistent vascular spasm? We have seen that the epinephrin theory is without verification. Were it proved, it would explain only the

mechanism, not its cause, and carry the problem one step further back. Many experienced clinicians have believed that high blood pressure is in some way related to overindulgence in food, the abuse of tobacco, of coffee, and other poisons, and the sedentary life, which characterize the well-to-do in our western civilization. Allbutt's hyperpiesis expresses this view. The results of treatment sometimes lend strong support to it. In a recent case, for instance, a gentleman of sixty-two, who showed at the subsequent autopsy a very early stage of vascular kidney disease, underwent a Tufnell cure for thoracic aneurism. The systolic pressure fell from 220 to 125 millimeters, after a hemorrhage once reached 70 millimeters, and yet returned to 190 millimeters before death. Remarkable drops are seen in hospital patients after rest in bed with salt-poor diet; the pressure usually rises moderately as soon as activity is resumed. Such reports as that of Hecht¹⁰⁶ show how much the tension may be modified during sanatorium treatment in which muscular training, massage, bland diet, limitation of fluid and of salt, and abstinence from tobacco, spices, and coffee coöperate with freedom from home and business cares to reduce the activity of the constrictor mechanisms. How much of this is central, how much peripheral, and which of the many changes in external conditions and internal relations is preponderant in accomplishing the result, is not clear. But, again, some persons of abstemious life develop hypertension, and in most of these, treatment effects no marked or permanent change in the blood pressure.

A conspicuous feature in many of these patients is the variability of the pressure, especially the systolic pressure, within short periods, often from hour to hour (Hensen,¹⁰⁶ Israel¹⁰⁷). All the causes of slight elevation of pressure in the normal person produce exaggerated effects in them. Vasodilators also, such as the nitrites, usually evoke a prompt, though temporary, response. Only in rare cases do the vessels cease to react. My experience is in entire accord with Matthew,¹⁰⁸ Miller,¹⁰⁹ and Wallace and Ringer,¹¹⁰ in this respect. Intercurrent acute disease usually produces a marked fall. These facts

show clearly, I think, that disturbed vasomotor regulation, not permanent vascular obliteration, is the usual important factor. Volhard¹⁰⁰ makes the interesting observation that this type of disease is very rare in Japan, and future statistics of vegetarian races may help to fix responsibility.

Gout and hypertensive nephritis are usually associated, and the clearing up of the causation of gout will illuminate our problem. One poison, however, which in rare cases produces acute gout, is the single cause of hypertensive cardiovascular disease upon which we can definitely put our fingers. That poison is lead. Vaquez¹¹¹ and Pal¹¹² have shown that lead colic is as truly a vascular crisis with transient hypertension as it is an intestinal cramp with constipation. As acute lead poisoning is thus a cause of marked acute vascular hypertonus, and chronic lead poisoning is known to be prolific of permanent hypertension, arteriosclerosis, and contracted kidney, one is strongly tempted to believe that the eventual anatomical vascular lesions are the sequel of the persistent vascular overstimulation. The suggestion, then, arises that other poisons, as yet unknown, act in a similar manner upon the blood-vessels. To carry the train of thought further is unprofitable, and such poisons must be isolated and their actions demonstrated before such a theory can be useful. That in most cases of high blood pressure they are not retention products in the ordinary sense is clear, as gross retention does not exist in these patients until late.

The theory of intoxication by substances held back by the damaged kidney cannot be entirely discarded, however. The observation of cases with partial or intermittent ureter obstruction taught Cohnheim¹¹³ long ago that hypertrophy of the heart and high arterial pressure might result. I have seen excision of the only functioning kidney lead to a rise in blood pressure, four days after, to 180 millimeters; it fell again toward death. Pässler¹¹⁴ and Brasch¹¹⁵ report interesting cases of long-standing anuria, due to bilateral ureter compression by pelvic carcinoma in women, with marked hypertension. One case of Brasch's rose from 115 to 210 millimeters after three days of anuria. In these instances, neither œdema nor

true uræmia occurs, but acute hypertension is the rule. They seem quite analogous to the results of experimental quantitative reduction of kidney substance. Whether this is due to normal metabolites, or abnormal compounds, is not clear. Pearce's¹¹⁶ interesting observations on the depressor substance of dog's urine suggest the possibility that a normal balance between pressor and depressor substances in the blood may be maintained by the kidney.

I believe that the rise in blood pressure which may accompany anuria in such toxic necroses of the kidney as are produced by bichloride of mercury, for instance, belongs in the same category. Krehl¹¹⁷ says this does not occur, but I have seen the pressure rise from 130 millimeters on the first day to 168 millimeters on the fifth day of bichloride poisoning, remaining about 170 millimeters until the ninth day; and then fall until death on the thirteenth. Friedrich Müller reports a similar finding.

I believe it is also probable, from some conspicuous instances of improvement following prostatectomy, that the effect of long-standing obstruction of the urethra may be the superposition of a blood-pressure rise of this type on an already existing hypertension. A few other cases that I have seen possibly fall into this category of quantitative renal insufficiency. I have in mind a patient with blood pressure of 200, who at autopsy showed complete infarction of one kidney, and only chronic passive congestion of the other. A second patient had a rudimentary kidney on one side, with moderate, diffuse nephritis of the other; he died with explosive uræmic symptoms. I have also seen cases of gradual destruction of the kidney by bilateral pyonephrosis, with hypertension and terminal uræmia. In the later stages of decompensated valvular disease, it is the rule to find the blood pressure above the normal, sometimes considerably so; and the sulphonphenolphthalein test gives evidence of a marked impairment of kidney function. Such patients frequently die with cerebral symptoms, much like those seen in uræmia. From the functional, as contrasted with the anatomical standpoint, it seems that chronic passive congestion

may produce serious disturbances in the kidney, and that the hypertension seen in such cases may be dependent upon this factor.

It is well known that patients with congenital cystic kidneys in the end develop the clinical picture of contracted kidney, with hypertrophied heart, high pressure, and low gravity urine. I have seen a striking example of this kind. One is tempted to think of the terminal state as one of quantitative reduction of kidney substance to the danger point, and in so doing to strengthen the argument for a more definite relation between kidney function and hypertension than the consideration of the atherosclerotic group seems to warrant.

The rare cases of amyloid disease must be considered for the moment an insoluble mystery. The kidneys are the seat of the most extensive vascular lesions, with practically every glomerulus infiltrated with the waxy substance. Polyuria may be present early, but in pure cases there is no hypertension, and in many there is actually an extreme, subnormal pressure. I have observed two autopsy cases in which the pressure ran from 65 to 90 millimeters for weeks. A satisfactory theory of nephritic hypertension must afford an interpretation of such phenomena. Were I convinced of the universal applicability of the epinephrin theory, I should believe that the extensive infiltration of the adrenals with amyloid, which is the rule when the other viscera are waxy, was a ready-made explanation. One cannot deny that this suggestion has a certain plausibility on its face; I offer it as it has occurred to me, without caring to infer much from it either way, until we have more positive evidence as to the relation of the adrenals to normal vascular tonus. I do not consider that the cachexia of these patients is adequate to account for their low blood pressure, though it may be one factor. From the functional standpoint it is important to note that the type of disturbance manifested by the amyloid kidney is usually that of obstinate oedema, with marked salt retention. Now, of the types of true chronic glomerulotubular nephritis least often associated with any change in the heart or blood pressure, the dropsical form stands out pre-eminently; and

vice versa, hypertension is most extreme in those nephritis who exhibit no oedema.* We are as yet quite too ignorant of the relations of the various excretory functions of the kidney, one to another, to base any theory upon such relations. Widal's¹¹⁰ classification of the nephritides into albuminuric, hypertensive, hydropigenous, and nitrogen retention types, while suggestive in its broad outlines, does scant justice to the infinite variety of nature. Such studies, however, as he has conducted with regard to functional disturbances in the kidney, and especially such accurate analyses of disturbance in the excretion of individual substances as Schlayer and his co-workers¹²⁰ have carried on, point the road toward our goal.

Observations of the blood pressure in true acute nephritis, a condition which even pathologists agree is entitled to its name, are scanty. Many observers have failed to find definite hypertension, but one can never be quite sure how marked the nephritis was. Certainly a moderate, though very definite, rise in blood pressure has in my experience accompanied severe acute nephritis in the few patients that I have been able to observe carefully. A particularly instructive case had a rise to 165 millimeters during the first week in bed, with a rapid fall as diuresis was established. He recovered completely, and my subsequent observations for almost six years have shown a constant pressure of between 115 and 125 millimeters. Recently, a boy in the hospital who had acute nephritis following severe tonsillitis, came in with a pressure of 190. He had slight general oedema, and a sulphophenolphthalein output of 54 per cent. In five days his pressure had fallen to 100, the oedema had disappeared, and the phthalein output had risen to 62 per cent. Rolleston¹²¹ has recently reported a transient rise in blood pressure in 12 out of 33 cases of scarlatinal nephritis, mostly mild; the highest pressure reached was 150. Kurt Weigert¹²² saw a pressure of 240 millimeters in severe post-scarlatinal nephritis fall to 170 millimeters before death. One of the most

* A recent case, however, has shown practically complete absence of sulphophenolphthalein excretion; so the functional impairment was evidently profound.

striking observations was that of Butterman,¹²³ who observed a rise of 50 millimeters within twenty-four hours from the onset of an acute scarlatinal nephritis. This is analogous to the stormy onset with initial uræmic convulsions that one observes occasionally.

The subacute and chronic types of glomerulonephritis which, from Löhlein's⁹⁹ studies especially, we may feel justified in grouping with the acute inflammations of the kidney, are somewhat variable in their effects on blood pressure. I have seen subacute nephritis with obstinate oedema and anæmia and a practically constant blood pressure, scarcely ever above the normal. In the chronic cases with terminal uræmic symptoms, the pressure often runs very high, though just before death it may show an extreme fall; in one case that I observed the fall was from 240 to 100 millimeters during the last twenty-four hours of life. A number of these patients show marked atrophy of the kidney and belong in the group of secondary contracted kidney. Until recently, they have not been differentiated from the general group of contracted kidneys. In practically all *post-mortem* statistics they tend greatly to increase the proportion of cases with small kidneys in which marked cardiac hypertrophy has been lacking. Such individuals frequently have dilated and hypertrophied hearts and general dropsy in addition to the uræmic symptoms. Roth¹²⁴ has described some of these patients with normal or scarcely increased blood pressure and no changes in the small or large blood-vessels. As a rule, the blood pressure rises progressively as serious uræmic symptoms supervene.

Uræmic hypertension, a hypertensive crisis accompanying the acuter cerebral manifestations, amaurosis, etc., to which Pal¹¹² has devoted so much attention, is an undoubted clinical fact. It is in every respect similar to the behavior of the blood pressure in puerperal eclampsia (Vaquez,¹²⁵ Vogeler¹²⁶). Lead poisoning may also give rise to analogous symptoms. Briggs¹²⁷ has described hypertensive crisis in arteriosclerotic subjects. It is such sudden and short-lived accessions of blood pressure that to me most strongly suggest increased activity of the adrenals. The search for epinephrin in the general circulation

should be made especially during such periods. Free venesection is the ideal treatment; its effects are shown on the blood-pressure chart as clearly as in the behavior of the patient.

Unfortunately, I must pass with mere mention the frequent association of increased blood pressure with exophthalmic goitre and uterine fibroids, the development of permanent hypertensive disease in women after the menopause and in many elderly diabetics, the occurrence of symptoms of hyperthyroidism in chronic nephritis. All these are facts suggestive of a relationship between disturbances of the internal secretions and vascular hypertonus, though admitting of far more than one explanation. Perhaps it is well that the limitations of one lecture prevent excursions into this field.

III. CONCLUSIONS

To assemble all the facts, as I have tried to do, is surely one of the most melancholy things in the world, as long as these facts remain unrelated. No one cares to look at a pile of bricks and stones, but as soon as these take their places in the structure for which they were shaped and assume those relations which were not seen so long as they remained mere building material, they take on real interest. The first step toward the construction of a scientific theory must always be the assembling of the materials, the next their scrutiny, to see how the parts may be fitted, one to the other. The building of the theory comes last, and in the field under discussion must be left for the future. The facts I have outlined, however, impress me as falling logically into certain large groups. In conclusion I shall tell you my present views about them.

I cannot entirely agree with Krehl¹²⁸ that, in the main, nephritis as such has no influence on the circulation. To me, heart, arteries, and kidneys seem to stand in an intimate relationship, one to the other; the influence of the kidney upon the circulatory system appears as unequivocal as the influence of the circulatory system upon the kidney. A disturbance in either may lead to results, which from the functional standpoint are indistinguishable, though the anatomical pictures be diverse.

If the study of experimental nephritis has taught us anything, it is this—that the degree and kind of impairment of kidney function can in no wise be inferred from the histological changes discoverable in the kidney by our present methods.

The symptom of hypertension in renal disease can, I believe, arise in three ways:

1. Hypertension may arise through purely quantitative reduction of kidney substance below the factor of safety. It is difficult to conceive of this as other than a vascular hypertonus due to retained poisons of some kind. Its clinical paradigm is the hypertension accompanying bilateral ureter obstruction, or the unfortunate surgical removal of the only functioning kidney. Possibly, it is one factor which helps to produce hypertension in the contracted kidney.

2. Hypertension may arise in connection with the unknown intoxication which causes disturbances of the central nervous system and which we call uræmia. This intoxication is not one of retention, in a strict sense, though it is most commonly present in those cases of advanced nephritis which manifest marked nitrogen retention. Clinically, it is associated with severe acute nephritis, sometimes at its very onset, besides the subacute and chronic inflammatory affections of the kidney.

3. Hypertension may arise in primary irritability of the vasoconstricting mechanism from unknown, probably extra-renal causes, which lead eventually to arteriolar sclerosis. In this type the disease in the kidney is the sequence, not the cause, of the generalized vascular lesion. When it progresses to a condition of extreme atrophy, resulting in the true primary contracted kidney, a renal element may be added to the existing hypertension. In some cases, arteriosclerosis of the larger vessels may spread peripherally and produce a similar form of disease. In these primary vascular diseases it is probable that eventual, widespread narrowing of the arterial stream bed in some cases produces a permanent, organic increase in peripheral resistance.

What are the vascular poisons back of these types of hypertensive disease? That question no one can answer. That epine-

phrin may be one of them is possible; that it is the only one seems to be improbable. One may say the same for the secretion of the hypophysis. I believe it is likely that different poisons produce different types of hypertension. One toxic cause we can name with certainty, lead. Excessive stimulation of the central vasomotor mechanism must also play some part in producing the varied clinical picture.

The first and second types of hypertension may at any time be superimposed upon the third. While the second, the uræmic type, must be considered dangerous in itself, hypertension in the arteriosclerotic or atherosclerotic kidney is best regarded as a compensatory effort of the organism, as Bier¹²⁰ first suggested, to be interfered with only when danger threatens, either of cardiac failure or of cerebral hemorrhage.

In functional pathology, nephritis to-day presents the aspect of a threefold problem—the problem of oedema, the problem of uræmia, and the problem of hypertension. The first is well on the road to solution, and in practical therapeutics has lost most of its difficulties. Of the second, we have barely scratched the surface. The third, seventy-five years after the first clear statement made by Bright, still baffles our best attempts at solution. That it will yield up its secrets through the increasing application of exact physiological methods at the bedside and through the discovery of means for reproducing the lesions of chronic nephritis in animals, I confidently believe. Then, and not till then, may we hope for the final merging of morphology and physiology in a higher synthesis. The finished picture of nephritis will then appear the same from either aspect: all specialization of function basing itself upon known differentiation of structure, and every alteration of structure manifesting itself by intelligible disturbance of function. It is the task of clinical medicine to effect this final reconciliation, for only the clinician must at all times look at disease from both points of view. In accuracy of observation and refinement of technic, the medicine of that day may surpass ours by far more than our laboratories surpass the meagre equipment of Guy's of seventy-five years ago; but the method will still be the method of Richard Bright,

the careful comparison of the symptoms studied during life with the lesions found after death.

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THE SIZE OF ORGANISMS AND OF THEIR CONSTITUENT PARTS IN RELATION TO LONGEVITY, SENESCENCE AND REJUVENESCENCE *

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I. BODY SIZE

BODY size is one of the most variable properties of organism; the smallest living things are probably invisible to the highest powers of the microscope, the largest are gigantic beasts weighing many tons. Within the same class, and in animals equally complex in structure, variations in size are enormous, as, for example, in the elephant and the mouse. Within the same species, where structural differences are insignificant, size differences may be very great. In some species there are great differences of size between males and females; in extreme cases males may be minute and rudimentary forms, without mouths and alimentary canals, and capable of living for only a few hours, as in certain rotifers, worms and arthropods, whereas the females are relatively large and perfect individuals capable of an extended existence.

In *Crepidula*, a genus of marine gasteropod which I have studied and to which I must particularly direct your attention, I have found¹ great differences of body size in the mature individuals of different species and also in different individuals of the same species. The volume of the average adult male of *C. fornicata* is 125 times that of the average male of *C. convexa*; the volume of the female of the former species is 32 times that

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¹ Conklin: Body Size and Cell Size, Jour. Morph., 12, 1912.

of the latter. In these gasteropods the males are always much smaller than the females; the volume of the average female of *C. plana* is about 15 times that of the average male. All mature animals of this genus are sedentary, and many of them live in or on dead shells which are the homes of hermit crabs. In the species *C. plana* I have found an interesting class of dwarfs; the animals of usual size live in large shells inhabited by a species of large hermit crabs (*Pagurus bernhardus*); the dwarfs live in small shells occupied by a species of little hermits (*Pagurus longicarpus*). The dwarfs are sexually mature and, unless forcibly removed, live their whole life long in the small shells, where they attain an average size only one thirteenth that of the normal forms, but if the dwarfs are forcibly taken out of the small shells and put into larger ones they may grow to be as large as animals of typical size. These dwarfs are, therefore, only a physiological variety, produced by environmental conditions.

What are the causes of such differences in size of animals of the same species? What explanation can be offered for the enormous difference in size between an elephant and a mouse? What are the factors generally involved in determining size?

1. There is plainly an inherited factor in all specific differences of this kind. Every species of animal and plant has a more or less characteristic body size which may be said to constitute the norm of that species. This norm may be altered to a certain extent by environmental conditions, but such possible modifications are relatively slight; no amount of environmental influence could ever make a mouse grow to the size of an elephant. The limits of body size of a race or species are as certainly inherited as are any other characteristics; their causes, whatever they may be, are intrinsic in the constitution of the germinal protoplasm.

What is the nature of this inherited factor which determines the possible size of organisms? Undoubtedly it is found in the power of growth as contrasted with limitations to growth, with the rate and duration of assimilation as contrasted with dissimilation. Increase in size may be due to mere imbibition of

water, or to an actual increase in the quantity of protoplasm, and of formed products, in the body. In this discussion the latter process alone will be termed growth. As long as assimilation exceeds dissimilation organisms grow, when the one balances the other they remain unchanged in size, when dissimilation exceeds assimilation they dwindle. The large-sized *Crepidulae* continue to grow for a much longer time than the small-sized ones. A mouse achieves its full growth after about 60 days and may live approximately 60 months; an elephant continues to grow for about 24 years and may live approximately 150 years.

What it is which keeps up this process of growth so much longer in one species than in another we do not know—and as so often happens, it is precisely this which we most desire to know, for length of life as well as size of body depends primarily upon the rate and duration of assimilation. It may be that there is some peculiar secretion or enzyme which stimulates growth and varying quantities of which cause one species to continue to live and grow for a much longer time than another species; it may be that some substance is formed in the course of development which limits growth and that it appears earlier in some species than in others. Since assimilation and dissimilation are chemical processes it is very probable that the factors which determine rate and duration of growth, and consequently body size and length of life, are of a chemical nature. This is a subject upon which there has been much speculation and but little work and to which experimental investigation might well be directed with promise of important results.

2. Another supposed factor which is not precisely hereditary nor yet strictly environmental is the size of the germ cells, of the "Ausgangszellen," from which an animal develops. Morgan² and Chambers³ found that small eggs of the frog give rise to smaller tadpoles and to smaller frogs than do large eggs.

² Morgan: Relation between Normal and Abnormal Development, etc., Arch. Entw. Mech., 18, 1904.

³ Chambers: Einfluss der Eigrösse, etc., Arch. mik. Anat., 72, 1908.

Popoff⁴ maintains that spermatozoa as well as ova vary in size, owing to slight inequalities of division during the genesis of these cells, and he supposes that when a large egg is fertilized by a large spermatozoon a large individual results, whereas if the sex cells are smaller than usual the individual developing from them will also be smaller. In favor of this hypothesis may be cited the fact that small eggs of *Rotifera*, *Phylloxera* and *Dinophilus* give rise to small and rudimentary males, whereas the larger eggs give rise to relatively large females. Within the same species, where the mode of development is the same for all individuals, egg size may be a factor in determining body size, but it is a relatively unimportant factor, since the size of an animal depends not merely upon its initial size, but chiefly upon the rate and duration of its growth. In many cases the smaller egg continues to grow for a longer period than does the larger one and in the end gives rise to a larger adult. This is strikingly shown in different species of *Crepidula*, where species with small eggs give rise to large animals and those with large eggs give rise to small animals. The large eggs produce large embryos, and the small eggs small embryos, but the latter continue to grow for a much longer period than the former and in the end give rise to animals of much larger body size than those which come from the large eggs. An egg of *C. fornicata* is about one quarter the volume of one of *C. convexa*, but the adult female of the former species is about 32 times the volume of one of the latter species, while the males of the former species are 125 times the volume of those of the latter species. Other cases of a similar sort are known and they show that in different species egg size cannot be correlated with body size, and even within the same species it is a relatively unimportant factor in determining size.

3. It is well known that many extrinsic factors influence the character, rate and duration of metabolism, and consequently the size of organisms. Among these extrinsic factors I shall mention only a few which are known to be important, namely,

⁴ Popoff: Experimentelle Zellenstudien, Arch. Zellforschung, 1, 1908.

(a) quantity and quality of food, (b) secretions of certain glands, particularly the sex glands, thymus, thyroid, and hypophysis, (c) various chemical substances, such as ether, alcohol, tobacco, lecithin, etc., (d) temperature, (e) oxygen, (f) presence or absence of waste products, (g) conditions of normal or abnormal stimulation and irritability. These extrinsic factors which influence growth have been studied by many investigators, but owing to lack of time I shall pass over all of them except the last named. In the case of the dwarf *Crepidula* which are found in the small shells with the small hermit crabs there is practically no evidence that any of the other factors, except the last named, are involved in this dwarfing. These animals live in open shells on sandy sea beaches along with the giant forms; so far as I can determine, the food supply is superabundant, while the conditions of temperature, aeration and freedom from waste products are identically the same for dwarfs and giants. The only difference which I have been able to detect is the size of the shells to which the animals are attached; those which are attached to the small shells of *Nassa* or *Litorina* live and die as dwarfs, reaching only about one thirteenth the volume of those which are attached to the larger shells of *Natica*; however, if they are removed from the smaller shells and placed on the larger ones they may grow to typical size. The dwarfs, however, are continually hampered by their limited quarters; they are unable fully to expand the foot or the mantle, and they are more frequently irritated by the movements of the hermit crabs than are those in the larger shells. Under these circumstances they probably take less food than those in larger quarters, and although they become perfectly differentiated and sexually mature they are dwarfed in size. Similarly I have found that *Paramecium* confined in capillary tubes never grows nor divides, though it may live indefinitely, and although precautions may be taken to change the medium frequently and thus to remove waste products and to supply abundant food and oxygen. In such tubes *Paramecium* is continually irritated and presumably takes less food than when in unconfined spaces.

II. BODY SIZE, CELL SIZE AND CELL NUMBER

Is the size of an organism due to the size of its constituent parts, or to the number of those parts, or to both of these causes combined? Evidently different organisms differ in this regard. In many plants and lower animals the number of constituent parts is directly correlated with the body size; branches and leaves, segments and organs may increase in number indefinitely with the growth of the organism. In tapeworms and many annelids the number of segments, with their characteristic organs, increases throughout life; but in more highly differentiated forms the number of body segments and organs is constant, and does not increase in number after embryonic stages. In spite of the information occasionally conveyed by examination papers, the number of bones or other organs in the human body does not depend upon the size of the man.

In animals in which the number of organs is constant the constituent parts of such organs may vary in number with the size of the organs. Thus in a large *Crepidula plana* the gill is composed of more than two hundred large filaments, in a dwarf it consists of only fifty or sixty small ones. The liver, sex glands and salivary glands are composed of a larger number of lobules in large animals than in small ones, and the size of each lobule is also larger. Evidently the number of such body parts, whether segments, organs, filaments or lobules, depends upon the power of growth and subdivision of each of these parts. In general the more complex any part becomes the less capable it is of subdivision, and so in all highly differentiated animals we find the body parts and organs are constant in number, though variable in size; whereas in lower animals the number of body parts as well as their individual size may vary with the size of the body as a whole.

Cells are generally recognized to be the ultimate independent units of organic structure and function; the causes of growth and differentiation, of assimilation and dissimilation, of longevity, senescence and rejuvenescence are to be looked for in cells. What is the relation of body size to cell size and cell

number? A large number of investigators have studied this problem in a wide range of animals and plants, and with apparently conflicting results; nevertheless enough is now known, I think, to permit a general answer to this question. Just as in the case of body parts and organs, so also with cells, complexity of differentiation and power of division are generally in inverse ratio. In many animals and plants certain types of cells continue to divide throughout life, whereas other types cease to divide at an early age. In both plants and animals those cells which continue to divide throughout the growing period become more numerous in large organisms than in small ones, but not individually larger; on the other hand cells which cease to divide at an early stage in the life cycle become individually larger in large animals than in small ones, though in closely related forms their number may remain the same. In short, the size of cells is directly proportional to the rate and duration of growth and inversely proportional to the rate of division. It is well known that muscle cells and nerve cells cease to divide at a relatively early age, whereas epithelial and gland cells, mesenchyme, blood and sex cells continue to divide for a longer period, if not throughout life; accordingly, one would expect to find that muscle cells and nerve cells are larger in giants than in dwarfs, but that the other types of cells named would differ in number but not in size—and this is the general result reached by most of the investigators who have worked on this subject (Donaldson, Levi, Boveri, Conklin, and others). In the most highly differentiated cells (muscle, nerve) growth takes place independently of cell division; in less highly differentiated cells (epithelium, mesenchyme) the two processes go hand in hand.

It is an important fact that growth in size and growth in complexity are separable processes, for although they are usually coincident during embryonic development they are not causally united. Just as growth in body size may, or may not, be accompanied by growth in complexity, so cell division may, or may not, be accompanied by differentiation. Cell divisions may thus be classified as differential and non-differential; the

former are associated with growth in complexity as well as in size, the latter with growth in size only; the former are relatively constant in number for a given species, the latter vary in number with the size of the individual. The earlier cleavages of the egg are more generally differential than are the later ones, and within the same genus and even in related genera and phyla the number and character of differential cleavages are very constant. Thus in all annelids and mollusks, with the exception of cephalopods, the ectoderm comes from three quarters of cells which are cut off, one after another, at the animal pole of the egg, and in all cases each of these quartets gives rise to homologous regions of the larva of the different forms; the left posterior member of the fourth quartet (*4d*) is the mesentoblast and in all annelids and mollusks (except cephalopods) it gives rise to the mesodermal bands and to the posterior part of the intestine; and in general, homologous portions of larval or adult animals come from homologous portions of the eggs of these animals through the medium of homologous differential cleavages.

On the other hand, non-differential cleavages are relatively inconstant in number, position and character; they vary greatly in number in different species, or even in different individuals of the same species, depending upon the size of the egg or embryo. Thus in different species of the genus *Crepidula* the differential cleavages are almost precisely the same in all, though the relative volumes of the eggs of different species vary from 1 to 27, but the non-differential cleavages are much more numerous in the large eggs than in the small ones. It is the fact that the earlier cleavages of eggs are so generally differential that makes possible the study of cell-lineage; if such cleavages were generally non-differential they would be relatively inconstant and lacking in significance.

In animals with determinate cleavage of the egg the number and nature of the cells at any given stage of differentiation is, under normal conditions, absolutely constant for each species, and it may be a constant number even for different species of a genus, especially if the eggs of the different species do not differ

greatly in size. In various ascidians (*Styela*, *Ciona*, *Molgula*, *Phallusia*, *Ascidia*) there is a close correspondence in the character and number of the cleavage cells present at corresponding stages of development, even up to advanced stages. For example, in all these genera there are 118 cells present when the cup-shaped gastrula is first formed and the prospective fate of each of these cells is indicated herewith: 10 will give rise to endoderm cells, 12 to muscle cells, 16 to mesenchyme cells, 8 to chorda cells, 8 to neural plate cells, 64 to ectodermal epithelium.

At the stage when the gastrula begins to elongate there are 218 cells distributed as follows: 26 endoderm cells, 12 muscle cells, 20 mesenchyme cells, 16 chorda cells, 40 neural plate cells, 104 ectodermal epithelial cells.

Each of these cells is characteristic in position, structure, size and potency, and this is true of all species and genera of simple ascidians hitherto studied with respect to this matter.⁵

In a number of species of small body size Martini^{6,7,8} has determined that there is a high degree of constancy in the number of cells in the adult body. In the appendicularian *Fritillaria pellucida* the number of cells is constant in the following organs: 28 flattened epithelial cells of body, 446 oikoplasts (columnar epithelial cells of body), 10 large gland cells in the tail, 7 flattened epithelial cells of the pharynx, 10 large cells of the endostyle, 24 small cells of the endostyle, 4 branchial gland cells, 7 branchial cells, 6 ciliated funnel cells, 19 epithelial cells in the stomach, 10 epithelial cells in the pylorus, 17 epithelial cells in the small intestine, 12 epithelial cells in the large intestine, 6 or 7 epithelial cells in the rectum, 39 cells in the brain, 25 cells in the chief caudal ganglion, 23 cells in the re-

⁵ Conklin: The Organization and Cell Lineage of the Ascidian Egg, *Jour. Acad. Nat. Sci., Phila.*, 13, 1905.

⁶ Martini: Die Konstanz histologische Elemente bei Nematoden, etc., *Verh. Anat. Gesell.*, 22, 1908.

⁷ Darwinismus und Zellkonstanz, *Sitz. u. Abh. naturforsch. Gesell. Rostock*, 1, 1909.

⁸ Studien über die Konstanz histologischer Elemente, I., II., III., *Zeit. wiss. Zool.*, 92, 94, 1909; 102, 1912.

maining nerve cord, 8 nuclei in heart and pericardium, 20 muscle cells, 12 large chorda cells, 4 small chorda cells. In different individuals of this species there is a high degree of constancy in the number of these cells, the only variation being in the occasional presence or absence of a single subdivision of a cell.

Also in the rotifer *Hydatina senta* he finds that there are all together just 959 cells, or rather nuclei, in the entire body of the adult, and that each organ consists of a perfectly characteristic number of cells. Even in different species of rotifers the number of cells in many homologous organs is the same; thus there are generally 6 cells in the anterior part of the oesophagus, 6 pairs of cells in the excretory tubules, and 13 cells in the cingulum, one of which is on the dorsal mid line.

In the nematode *Ascaris megalcephala* Goldschmidt ⁹ found 162 cells in the nervous system, while Martini ⁸ finds 65 muscle cells in *Oxyuris*, and 87 muscle cells in *Sclerostoma*, the latter being derived from 65 cells of an earlier stage.

A similar constancy of cell number has been found by Woltereck ¹⁰ in *Polygordius* larvæ, by Apathy in the central nervous system of *Hirudinea*, by Gaule and Donaldson ¹¹ in spinal ganglia of frogs, and by many investigators in small but highly differentiated parts, such as the ommatidia of compound eyes, the lens fibres of vertebrate eyes, the nurse cells of certain arthropod and annelid ova, and so on. Such cases of cell constancy are, as Martini remarks, "the crowning fact of determinate development." In all such cases the definite number of cells in the entire body or in a particular organ must be determined by a definite number of cell divisions which proceed from the egg, or from the protoblast of the organ, and this limitation in the number of cell divisions must in some way be determined

⁹ Goldschmidt: Das Nervensystem von *Ascaris* etc., Zeit. wiss. Zool., 90, 1908.

¹⁰ Woltereck: Beiträge zur praktischen Analyse der *Polygordius*-entwicklung, Arch. Entw. Mech., 18, 1904.

¹¹ Donaldson: The Growth of the Brain, Scribners, New York, 1895.

by heredity. Since increase of differentiation is associated with decrease of cell division, the latter being stopped altogether when differentiation has reached a certain stage, it seems probable that all cases of cell constancy are due to constancy of differentiation.

Where the number of cells in an organ or in an animal is very large it is not possible to prove that the cell number is constant, but in many cases where cell division ceases during embryonic stages the cell number is constant. In such cases cell division does not continue after differentiation is complete, though cell growth does. To all such cases in which there is cell constancy Martini gives the name "Eutelie."

On the other hand, there are many animals in which the number of cells in any particular organ is not constant but is proportional to the size of the organ. In *Crepidula* the number of egg cells within the ovary and the number laid in any season varies with the size of the animal, but the size of individual eggs remains constant for each species; the same is also true of epithelial cells, gland cells and blood cells. The divisions by which such cells are formed are in general non-differential, and since both growth and division in such cases continue throughout life the size of any given type of cell is fairly uniform whatever the body size may be. In differential cell divisions, or in highly differentiated cells which do not continue to divide throughout life, the size of cells varies directly with the body size and with the infrequency of division.

III. CELL SIZE AND NUCLEAR SIZE

In a series of recent papers Richard Hertwig^{12, 13} and several of his pupils have maintained that there is a definite ratio between the size of the nucleus and the size of the cell; this is the "Kernplasmarelation," or the nucleus-plasma ratio. When this ratio is altered by the greater growth of the nucleus, Hertwig thinks that it leads to a "tension," which brings about

¹² Hertwig, R.: Ueber Korrelation von Zell- und Kerngrösse, etc., Biol. Centralbl., 22, 1903.

¹³ Hertwig, R.: Ueber neue Probleme der Zellenlehre, Archiv. Zellforschung, 1, 1908.

division, and thus the normal nucleus-plasma ratio is restored. This ratio is supposed to be a constant one under normal conditions, and if at any time it is altered it is capable of self regulation.

On the other hand, I¹⁴ have found that this ratio varies greatly in different cells of an animal, and, indeed, within the same cell at different stages of the division cycle; that it may be experimentally altered, and that it is a result, rather than a cause, of the frequency of cell division.

Within the same cell the size of the nucleus varies greatly at different stages of the division cycle, while the volume of the cell as a whole remains relatively constant. The nucleus is smallest during the anaphase, or later stages of division, when it consists of a compact plate of condensed chromosomes; it is largest immediately before the nuclear membrane dissolves at the prophase of the next division. In the cleavage of the egg of *Crepidula plana* the nucleus-plasma ratio in identically the same cell varies from approximately 1:6 when the nucleus is largest, to 1:286 when it is smallest; that is, the volume of the nucleus increases nearly 50 times during the resting period between the previous anaphase and the subsequent prophase; during this same time the volume of the cell remains practically unchanged.

Even when measured at the same phase of the division cycle the nucleus-plasma ratio differs greatly in different cleavage cells; at maximum nuclear size the volume of the nucleus of certain cells of *Crepidula* (4A-4C) may be 3 times that of the protoplasm, whereas in other cells (1A-1D) the volume of the protoplasm may be 14.5 times that of the nucleus. At minimum nuclear size the nucleus-plasma ratio may vary from 1:29 in the cells 1a²-1d², to 1:285.5 in the cells 1A-1D.

The growth of the nucleus between successive divisions is due to the absorption from the cell body of a particular kind of cell substance, which constitutes the achromatin of the nucleus; at the beginning of this growth the nucleus is composed of compact chromosomes, at its end it consists of a large vesicle of

¹⁴ Conklin: Cell Size and Nuclear Size, *Jour. Exp. Zool.*, 12, 1912.

achromatic substance in which the chromatin usually exists as scattered granules. At the next division some of these granules form chromosomes and all the rest of the nuclear content is liberated into the cell body, to be again absorbed by the daughter nuclei during the succeeding rest period. There is thus a sort of diastole and systole of the nuclear vesicle during every division cycle of a cell, chromatin being taken up by the nucleus during its growth and liberated again into the cell body during its division.

In different cleavage cells of *Crepidula plana*, when the yolk is eliminated from consideration, the maximum nucleus-plasma ratio varies from 1:0.37 to 1:14.5; that is, the volume of the actual protoplasm in certain cells may be only one-third the volume of the nucleus, or in other cells it may be fourteen times that volume, depending largely upon the length of the resting period.

In general the size of a nucleus is directly proportional to the volume of the general protoplasm in the cell, to the length of the resting period, and in cases of abnormal or irregular distribution of chromosomes, to the number and volume of the initial chromosomes which go to form the nucleus. The inciting cause of cell division is not to be found in departures from a normal nucleus-plasma ratio, which is a result rather than a cause of the rate of cell division, but rather in the coincidence of certain metabolic phases in nucleus, centrosome and protoplasm.

If the growth period of the nucleus is very long, the greater part of the protoplasm may be taken into the nucleus, as in those cleavage cells in which the nuclear volume is about three times as great as that of the protoplasm outside of the nucleus; if the growth period of the nucleus is short, the nucleus remains correspondingly small. If nuclear division is prevented, by hypertonic solutions or by decreased oxygen tension, the nuclei may grow to an enormous size until they contain the greater part of the cell protoplasm.¹⁵

¹⁵ Conklin: Experimental Studies on Nuclear and Cell Division, Jour. Acad. Nat. Sci., Phila., 15, 1912.

In certain stages of the division cycle it is possible by the use of hypertonic solutions to prevent the daughter chromosomes from absorbing achromatin, and in such cases these chromosomes form small, densely chromatic nuclei, while the achromatin may be gathered into one or many vesicles. In other cases, the chromatin may be caused to contract and to squeeze out the achromatin. The latter case is similar to that which takes place normally in the formation of a spermatozoon from a spermatid, where there is a condensation of the chromatin of the spermatid nucleus and a squeezing out of the achromatin; this diminution of the nucleus is coincident with the transformation of the protoplasm of the spermatid into differentiation products. A similar thing happens in superficial epithelial cells which are undergoing keratinization; up to a certain stage, the nuclei of such cells shrink in size and become more densely chromatic in proportion as the cell protoplasm is converted into metaplasma. The same thing is true of gland cells, muscle cells, fibre cells and fat cells in which the general protoplasm is progressively being changed into differentiation products, and coincidentally the individual nuclei shrink in size and become more densely chromatic.

In no case do metaplastic substances or differentiated structures of the cell enter into the nucleus during its growth, and the relative quantities of general protoplasm and of differentiated products in a cell can be determined by the size to which the nucleus will grow during interkinesis, under given conditions of time, temperature, and so on. By subjecting eggs to centrifugal force, the quantities of protoplasm and yolk in the cleavage cells may be greatly changed, and under such circumstances the size of a nucleus is always proportional to the volume of the protoplasm in which it lies; the heavier yolk which segregates at the peripheral pole, and the lighter watery or oily substance which gathers at the central pole of the centrifuged egg do not contribute to nuclear growth, only the clear protoplasm which lies in the middle zone enters the nucleus or contributes to its growth. In muscle cells with small nuclei, the quantity of general protoplasm (sarcoplasm) which may enter

into the nucleus or contribute to its growth is small; in nerve cells, it is evidently larger, since the nuclei of such cells are relatively large, but the substance which may enter the nucleus of a nerve cell is by no means as great in quantity as in germ cells and blastomeres, thus indicating that much of the substance of a nerve cell is too highly differentiated to enter into the nucleus. In epithelial and gland cells, the size of nuclei is limited not only by the presence of metabolic products in the cells, but also by the occurrence of cell division and the consequent limitation of the growing period of the nucleus.

The following table gives the cell diameter and nuclear diameter at maximum size; the corresponding nuclear volume; the cell volume less the nuclear volume; and the nucleus-cell ratio, in a number of different kinds of cells in adult individuals of *Crepidula plana*:

RATIO OF NUCLEAR VOLUME TO CELL VOLUME IN ADULT INDIVIDUALS OF *Crepidula plana*.

Kinds of cells.	Maximum diameter of cell. μ	Maximum diameter of nucleus. μ	Volume of nucleus. Cu. μ	Volume of cell less volume of nucleus. Cu. μ	Nucleus-cell ratio.
Spermatocytes I.....	8	6	113	155	1: 1.37
Spermatocytes II.....	7	5	64.4	114.6	1: 1.7
Spermatids (chromatin condensed).....	3	2	4.18	9.94	1: 2.38
Oocytes I (before yolk formation).....	10	6	113	407	1: 3.6
Large ganglion cells (not including any outgrowths).....	17×17×23	12	905	5724	1: 6.3
Ectodermal epithelium (of foot).....	6×6×15	5	65.4	474.6	1: 7.1
Epithelium of mantle (near anus).....	5×5×15	4	33	342	1:10.3
Intestinal epithelium.....	11×11×12	6	113	1339	1:11.8
Gastric epithelium.....	10×10×36	8	268	3332	1:12.4
Branchial epithelium.....	7×7×9	4	33	408	1:12.3
Liver cells (without secretion products).....	14×14×30	9	382	5498	1:14.4
Liver cells (with secretion products).....	15×15×45	6*	113	10012	1:88.6
Oocytes I (before maturation and with maximum quantity of yolk).....	150	42	32409	1722591	1:53

* Nucleus shrunken and irregular in shape.

The nucleus-cell ratio of these cells varies from 1:1.3 to 1:88.6, depending primarily upon the quantity of formed substance in the cells. The nuclei are relatively largest in germ

cells before the formation of yolk, and in embryonic cells in which there is relatively little formed substance; in such cases a relatively great part of the protoplasm may enter the nucleus. The nuclei are relatively smallest in those cells in which the protoplasm has been most completely transformed into products of metabolism or differentiation, such as gland cells filled with secretion, red blood cells of mammals in which the nuclei completely disappear, egg cells filled with yolk, and spermatozoa in which most of the protoplasm has been transformed into the contractile substance of the flagellum.

I have not been able to measure the volume of muscle cells in *Crepidula*, but such measurements have been made by Eycleshymer¹⁶ for the striated muscle cells of *Necturus*. From the measurements given by Eycleshymer, I have calculated the nucleus-plasma ratio in the usual manner, that is, by determining the ratio of the nuclear volume to the cell volume less the nuclear volume; and I find that in the 7 mm. and 8 mm. embryos this ratio is about 1:11, whereas in the 23 cm. adult it is about 1:73. The increase of cell substance is therefore less than seven times, instead of twenty or thirty times, that of the nucleus, as he states.

It is important to note that Eycleshymer found that as the fibrillæ are progressively formed out of the protoplasm of the cell, the nuclei are crowded out of the centre of the cell toward its periphery; that the nuclei become more densely chromatic, and especially so on the side of the nucleus toward the fibrillæ; and that possibly the nuclei may disintegrate and their chromatin go to form the dark bands of the striated muscle fibre. These facts seem to me to justify the conclusion which I reached in a former paper:¹⁴

It is probable that the contractile substance which makes up the larger part of the muscle cell does not contribute to the growth of the nucleus as does the protoplasm of embryonic cells—that so far as the growth of the nucleus is concerned it acts as does yolk, oil, membranes, fibres or other products of metabolism and differentiation. If only the

¹⁶ Eycleshymer: The Cytoplasmic and Nuclear Changes in the Striated Muscle Cells of *Necturus*, *Am. Jour. Anat.*, 3, 1904.

sarcoplasm of the muscle cell and not its contractile substance is able to contribute to the growth of the nucleus, the small volume of the nuclei as compared with the entire cell would find a ready explanation. There can be no doubt that the plasma is the chief seat of differentiation, as Minot has emphasized, and that highly differentiated cells, such as muscle, nerve, and some kinds of connective tissue, have a larger amount of plasma *and its products*, relative to the nucleus, than have embryonic cells. In the case of fibre cells, fat cells and probably muscle cells, the cell body becomes filled with the products of differentiation and metabolism, which like the yolk in egg cells, or the secretion products in liver cells, cannot enter the nucleus and consequently do not influence its size. In such tissue cells the cell body is relatively much greater as compared with the nucleus, than in purely protoplasmic cells, but I have been unable to find any evidence that the ratio of protoplasm (using this term in its usual sense) to the nucleus is greater in tissue cells of *Crepidula* than in the blastomeres.

Just as the size of a nucleus in any given species is proportional to the volume of the general protoplasm, so the volume of its chromosomes is proportional to the volume of the nucleus. The number of chromosomes and their relative sizes are characteristic for each species, but the absolute size of chromosomes in any given species depends upon the size of the nucleus from which they come. Throughout the period of cleavage, as the cells and nuclei grow smaller, the chromosomes also diminish in size. The view of Boveri¹⁷ that the chromosomes divide when they have grown to their original size before division, and that thereby a definite specific size of the chromosomes is maintained, finds no confirmation in the work of Erdmann,^{18,19} Schleip²⁰ or myself; while the view of Koehler²¹ that the autonomy of the chromosomes may be extended to their growth, which is sup-

¹⁷ Boveri: *Zellenstudien V.*, Jena, 1905.

¹⁸ Erdmann: *Experimentelle Untersuchungen der Massenverhältnisse, etc.*, Arch. Zellforsch., 2, 1908.

¹⁹ Erdmann: *Qualitative Analyse der Zellbestandteile, etc.*, Ergeb. Anat. Entw., 20, 1912.

²⁰ Schleip: *Das Verhalten des Chromatins, etc.*, Arch. Zellforsch., 7, 1911.

²¹ Koehler: *Ueber die Abhängigkeit der Kernplasmarelation, etc.*, Arch. Zellforsch., 8, 1912.

posed to be independent of that of other cell constituents, is flatly contradicted by the facts.

During the cleavage stages, at least, neither the nuclei as a whole nor the chromosomes double in volume at each successive division as is so often assumed. The total volume of the nuclei at the 70-cell stage of *Crepidula plana* is only 2.25 times their volume at the 2-cell stage. The volume of the protoplasm more than doubles, at the expense of the yolk, between the 1-cell and the 24-cell stages, while the total nuclear volume increases less than 1.5 times during this period. Jennings ²² has shown that the *rate* of growth is numerically greater than I had stated if one compares any stage with its immediately preceding stage, but, of course, this criticism does not apply to the total *actual* growth of nuclear material during any given period of development. It is often said that there is a "colossal increase of nuclear mass" but no increase in the protoplasm during the cleavage stages of the egg; and correspondingly there is said to be a great increase in the ratio of nucleus to plasma in the cleavage period. Upon this supposed increase in the nuclear material as compared with the plasma, Minot and Hertwig have based their hypotheses that the cleavage of the egg represents a period of rejuvenescence. However, in *Crepidula* and *Fulgur* among the gastropods and in *Styela* among ascidians there is no great change in the nucleus-plasma ratio during cleavage, and I believe that this will be found to be generally true for other animals. On the other hand, there is a considerable increase in the plasma at the expense of the yolk, during the cleavage period in these animals, and in this fact, rather than in an increase of nuclear substance, is to be found the cause of such rejuvenescence as may occur in these stages.

IV. LONGEVITY, SENESCENCE AND REJUVENESCENCE

Apart from accidental causes of death, longevity is determined by the duration of the excess of anabolism over catabolism. If destructive metabolic changes gain ascendancy over

²² Jennings: Nuclear Growth during Early Development, Am. Nat., 46, 1912.

constructive ones at an early period the organism is short lived; if constructive processes are indefinitely in the ascendant the organism is potentially immortal. Such a condition is shown in *Paramecium* where Woodruff ²³ has reared more than 3,000 generations without conjugation and without loss of vitality. These and other similar experiments have demonstrated the essential truth of Weismann's doctrine that protozoa are potentially immortal. Woodruff found that the most important factors for maintaining vigor are proper food and freedom from the poisonous effects of waste products. In higher animals there is no doubt that both of these environmental factors are important, but there are also other important factors, which influence length of life, which are not entirely environmental.

Duration of assimilation, conditions not merely body size, but also length of life. Very large animals are long lived and small ones are apt to be short lived, though the latter is by no means universally true—length of life being conditioned by duration of the ascendency of assimilation over dissimilation, whereas size is conditioned also by rate of assimilation as contrasted with dissimilation.

Weismann has pointed out a relation between longevity and the rate of reproduction—animals in which there is a slow rate of reproduction being in general long lived, while those in which the rate of reproduction is rapid are generally short lived. Numerous exceptions to this rule may be cited, though in many cases it is undoubtedly true; but Weismann has not proved that length of life is the result of slow reproduction. It may well be that both length of life and rate of reproduction are dependent upon the duration and rate of assimilation and dissimilation in somatic and germinal cells.

There is also an undoubted relation between longevity and adaptability, or the power of regulation. If life is continuous adjustment of internal conditions to external conditions, length of life may be said to depend upon the duration and perfection of such adjustment. The power of regulation is much less per-

²³ Woodruff: Dreitausend und dreihundert Generationen von *Paramecium*, etc., Biol. Centralb., 33, 1913.

fect in some animals than in others, and at certain stages of the life cycle than at other stages. But in all animals this power is greatest where the relative proportion of protoplasm to metaplasma, or differentiation products, is greatest, and where the protoplasm is most labile. In protozoa this power of regulation is shown at every division and it suffers no abatement in successive generations; in metazoa generally the power of regulation is greatest in early stages of development and in tissues in which protoplasm is abundant, and it diminishes as life advances and as the products of differentiation more and more replace the protoplasm. In the fission of a *Paramecium* there is a certain amount of dedifferentiation preceding division and of redifferentiation succeeding it, and as a result of this the two halves of the original *Paramecium* become alike; furthermore, in successive generations, there is no accumulation of the products of differentiation. In the division of the eggs of metazoa the cleavage cells sooner or later become unlike, owing to the differentiations present in the mother cell and the failure of complete regulation in the daughter cells. This progressive differentiation is accompanied by a progressive loss of the power of regulation, and when the general protoplasm is so completely transformed into differentiation products that the power of regulation is completely lost, the organism as a whole must lose the power of adjustment to external conditions, and hence of indefinitely continued life.

Many different hypotheses have been advanced to account for the running down of the vital machine. That death is not a necessary corollary of life is evidenced by the potential immortality of protozoa and of the germ cells of metazoa. Senescence, like all other processes occurring in organisms, is primarily a cellular phenomenon. The decline and degeneration of cells begins in the earliest stages of individual development; in many cases large numbers of germ cells regularly undergo degeneration, apparently as the result of intrinsic rather than of extrinsic causes. The polar bodies which are formed during the maturation of the egg are at the same time the smallest and the shortest lived cells in the entire life cycle; they rarely

last beyond the cleavage period and do not grow at all. Evidently their degeneration is due to lack of the power of assimilation, rather than to the accumulation of waste products, or to the increase of formed material. This lack of the power of constructive metabolism is evidently not due to lack of chromatin, for at the time of their formation they contain as much chromatin as the egg cell itself; they usually contain very little protoplasm, but even when the quantity of protoplasm in them is very greatly increased, through the effects of pressure or centrifugal force at the time of their formation, they still lack the power of assimilation and differentiation. Such a large polar body resembles an unfertilized egg, and like it is incapable of development unless stimulated by the entrance of a spermatozoon or by some artificial means.

In many cases certain cleavage cells run through their development quickly and then degenerate and disappear, while other neighboring cells live as long as the organism itself. Many larval or fetal organs have a very short life; the cells of which they are composed grow and divide rapidly for a time and then dissimilation exceeds assimilation and they dwindle and disappear. Throughout the mature life of any metazoan many cells are continually growing old and dying, while others take their places. Even in the oldest organisms certain types of cells are still young enough to grow and divide and there is no reason to doubt that such cells are potentially immortal and, if saved from the general death of the organism by isolation, might live indefinitely. Cells which continue to grow and divide throughout life apparently never grow old. It is customary to speak of the germ plasm as potentially immortal, but it is not generally recognized that other kinds of plasm may also be immortal. Indeed all kinds of protoplasm may be regarded as potentially immortal, except when processes of constructive metabolism are prevented in one way or another. In most cases the power of cell division is lost before that of growth, and the presence or absence of cell division is therefore indicative of youthful or of senile conditions in the cells concerned. Measured by this standard, certain cells grow old

at a very early stage in the life cycle, whereas others remain young until overwhelmed by the general death of the organism. Senescence then is not a uniform process for the entire organism; it begins in certain cells at a very early stage of development, while it may not appear at all in other cells.

The possible causes of senescence and rejuvenescence may be classified as structural and functional, though these two should not be regarded as mutually exclusive. Indeed, it is practically certain that both structure and function are involved in these processes as in most other vital phenomena. However, different students of this subject have placed emphasis more or less exclusively upon either the structural or the functional causes of senescence and rejuvenescence.

Under the structural causes may be cited Minot's hypothesis that senescence is caused by an increase in the amount of protoplasm as compared with the nucleus. In 1890 he ²⁴ summarized his views on this subject in the following words:

We have then to state, as the general result of the studies which we have just made, that the most characteristic peculiarity of advancing age, of increasing development, is the growth of protoplasm; the possession of a large relative quantity of protoplasm is a sign of age. . . . We see that there is a certain antithesis, we might almost say a struggle for supremacy, between the nucleus and protoplasm.

In several subsequent papers and books,²⁵ Minot has developed this idea at length. In his book on "Age, Growth and Death," ²⁶ he concludes that

Rejuvenescence depends on the increase of the nuclei, senescence depends on the increase of the protoplasm and on the differentiation of the cells.

R. Hertwig's ²⁷ views are apparently diametrically opposed

²⁴ Minot: On Certain Phenomena of Growing Old, Proc. Am. Ass'n Adv. Sci., 29, 1890.

²⁵ Minot: Ueber Vererbung und Verjüngung, Biol. Centralbl., 15, 1895.

²⁶ Minot: Age, Growth and Death, Putnams, New York, 1908.

²⁷ Hertwig, R.: Ueber die Kernkonjugation der Infusorien, Abh. Bayer. Akad. Wiss., II. Kl., 17, 1889.

to those of Minot. He finds that senescence or rather "depression" and "physiological degeneration," in *Actinospherium* and *Infusoria* are accompanied by an enormous growth of the nucleus. He regards the immature egg cell with its great nucleus as in a condition of depression similar to that found in the protozoa named. By the processes of maturation and fertilization this nuclear material is greatly reduced and thus the cells are brought back to a normal condition.

As opposed to the hypotheses of Minot and Hertwig, it may be pointed out that the larger part of a resting nucleus is composed of achromatin which has been absorbed from the cell body, and that the size of a nucleus depends chiefly upon the quantity of general protoplasm in a cell and upon the length of the resting period during which the nucleus is absorbing this protoplasm. So far from there being an antithesis between nucleus and general protoplasm, we find that the general protoplasm is common to both; small nuclei occur only in cells with a small amount of such protoplasm, while large nuclei occur only in cells with a large amount. It is not the increase in the general protoplasm which causes the nuclei to become relatively small, but rather the increase in the differentiation products and the corresponding decrease in the general protoplasm.

In most respects I am in hearty accord with Minot's latest formulation of the causes of senescence.²⁸ In this work he particularly emphasizes the effect of differentiation in causing senescence. Indeed, he concludes, "dass die Differenzierung als die wesentliche Ursache des Altwerdens zu betrachten ist." Nevertheless, he still holds that the greater growth of the protoplasm, relative to the nucleus, is the essential basis of differentiation; and that we may distinguish in development an earlier and shorter period, which is characterized by the preponderating growth of the nucleus, from a second and longer one characterized by growth and differentiation of the protoplasm—the former being the period of rejuvenescence, the latter the period of senescence. In *Crepidula*, as I have shown,¹⁴ the growth of nuclear material during early cleavage is not greater

²⁸ Minot: "Moderne Probleme der Biologie," Fischer, Jena, 1913.

than that of the protoplasm, and in general the size of a nucleus is directly proportional to the quantity of general protoplasm and to the length of the resting period, because general protoplasm is absorbed by the nucleus during interkinesis, whereas products of differentiation do not enter the nucleus. A causal explanation is thus given of the relation between nuclear size and cell size at different stages of development; and in the fact that differentiation products can not enter the nucleus we have, I believe, a causal explanation of the relation between differentiation and senescence.

The principal objection to Minot's formulation of the cause of senescence is that it overemphasizes the antithesis between nucleus and protoplasm and does not, with sufficient clearness, distinguish between the general protoplasm and its differentiation products. It is undoubtedly true that with advancing age and differentiation there is an increase of cellular as compared with nuclear substance, but the significant thing here is the fact that this cellular increase is not so much in the protoplasm as in the products which are formed from it and which cannot enter into the nucleus.

By all odds the most important structural peculiarity of senescence is the increase of metaplasma or differentiation products at the expense of the general protoplasm. This change of general protoplasm into products of differentiation and of metabolism is an essential feature of embryonic differentiation and it continues in many types of cells until the entire cell is almost filled with such products. Since nuclei depend upon the general protoplasm for their growth, they also become small in such cells. If this process of the transformation of protoplasm into differentiation products continues long enough it necessarily leads to the death of the cell, since the continued life of the cell depends upon the interaction between the general protoplasm and the nucleus. In cells laden with the products of differentiation, the power of regulation is first lost, then the power of division, and finally the power of assimilation; and this is normally followed by the senescence and death of the cells.

In some cases the progressive transformation of protoplasm into metaplasma may be reversed; in some manner the formed material is dissolved and converted into general protoplasm, the protoplasm and nuclei increase in size, the cells begin to divide and may become capable of regulation. In short, this reversal of the differentiation process leads to the rejuvenescence of senile cells. Minot ²⁸ holds that differentiated cells do not become undifferentiated—but at least it must be admitted they may lose their products of differentiation and metabolism; gland cells lose their secretion granules, egg cells their yolk, spermatozoa, within the egg, their flagella, injured muscle cells their fibrillæ, and so on. In such cases differentiation products are either eliminated from the cell or are transformed into a more labile and more general form of protoplasm, though the latter is probably not undifferentiated. I have used the term *dedifferentiation* for this process.

Among functional causes of senescence may be mentioned the well-known opinion of Metschnikoff, that the organism is slowly poisoned by its own waste products. Metschnikoff especially emphasizes the effects of intestinal fermentation and putrefaction in producing old age. Zoologists are familiar with the fact that, in certain Polyzoa and Tunicata which lack kidneys or efficient means of eliminating urea, or other nitrogenous waste, the tissues gradually become laden with such waste substances and the animal becomes senile and finally dies, but before this happens it may give off one or more buds which are relatively free from these waste products and which continue the life of the colony. It is a general phenomenon both in plants and animals that buds are composed of protoplasm which is not laden with products of differentiation or metabolism, and hence they exhibit youthful characteristics although the body from which they come may be senile.

Another functional cause of senescence is to be found in a decrease in the power of constructive metabolism. This factor has been recently advocated by Child ²⁹ in a very valuable

²⁸ Child: A Study of Senescence and Rejuvenescence, etc., Arch. Entw. Mech., 31, 1911.

paper, in which he concludes that anything which decreases the rate of metabolism, such as "decrease in permeability, increase in density, accumulation of relatively inactive substances, and so on," will lead to senescence. On the other hand, "Rejuvenescence consists physiologically in an increase in the rate of metabolism and is brought about in nature by the removal in one way or another of structural obstacles to metabolism."

It is well known that constructive metabolism cannot take place in the absence of a nucleus, and I have elsewhere¹⁴ shown that the interchange between nucleus and protoplasm is a condition of assimilation. I have likewise shown that only the general protoplasm can enter the nucleus and that the products of differentiation are excluded from it. The progressive increase of such products and corresponding decrease in the general protoplasm lessen this interchange between nucleus and cell body and thus decrease the power of constructive metabolism.

In conclusion it may be said that there are several factors which produce senescence, but that the chief of these is the progressive differentiation of the protoplasm. As Minot has well said, "Old age and death are the price which we pay for our differentiation." If we could find means by which this progressive differentiation could be stopped or reversed when it has gone too far, we might hope to attain potential immortality. That the possibility of this is not a mere delusion is shown by the fact that there are many animals which either in whole or in part are capable of rejuvenescence. In Protozoa the dedifferentiation which usually precedes or accompanies division is a process of rejuvenescence, and where such dedifferentiation and division are long delayed, even protozoans show signs of old age. The same is true of germ cells; the mature egg and sperm are senile cells not because the one has a very large nucleus and the other a very small one, but because both are loaded with products of differentiation which interfere with constructive metabolism. When the sperm enters the egg and either leaves behind its old cell body or dissolves it, and its nucleus gets a new protoplasmic body, it is rejuvenated; likewise, when the egg begins to dissolve the yolk and other products of differ-

entiation with which it has been loaded, it begins to live anew.

Similarly, any adult animal or plant which is capable of dedifferentiation is also capable of renewing its youth. It has long been known that encystment and accompanying loss of differentiation lead to rejuvenescence. Jacobs,²⁰ working under my direction, found that when the rotifer, *Philodina*, becomes senescent, it may be rejuvenated if it is completely dried up and afterwards put back into water; in this treatment it evidently undergoes dedifferentiation.

Child²¹ found that after planarians in a condition of apparent extreme senility had been starved for some time, they afterward became young within a few hours or days. Evidently the starving served to use up a part of the structural substance which prevented rapid metabolism. Similar conditions of renewed vigor are shown by many animals after long hibernation. The great breeding activity of many animals, such as frogs, so soon after their winter sleep, may find a physiological explanation in this using up of metabolic products during hibernation and the subsequent increase in vitality.

In similar manner it is known that the new tissue which is formed in regeneration comes from undifferentiated (epithelial or lymphoid) or from dedifferentiated cells (for instance, muscle cells of amphibia). In the latter case also there is a rejuvenescence, due to the loss of differentiation products. In this case dedifferentiation is evidently due, in the first instance, to the injury. It is at least possible that the failure to regenerate lost parts, which many animals show, is due to the inability of the cells to undergo dedifferentiation and subsequent rejuvenation.

In conclusion, we find that the life of a cell is dependent upon the continued interaction of nucleus and protoplasm; that as the protoplasm is transformed into products of differentiation this interaction of nucleus and protoplasm is reduced and constructive metabolism is diminished; that when the

²⁰Jacobs: The Effects of Desiccation on the Rotifer *Philodina roseola*, Jour. Exp. Zool., 6, 1909.

quantity of protoplasm present has been reduced beyond a certain point, either by its transformation into metaplasma, or by other means, constructive processes fail to compensate for destructive ones, and the cell grows old and finally dies. On the other hand, processes which lead to the increase of the general protoplasm in a cell, either by the growth of the protoplasm already present or by the conversion of metaplasma into protoplasm, lead also to the growth of the nucleus, to increased interchange between nucleus and protoplasm, and hence to increased powers of assimilation, cell division and regulation. Anything which decreases the interchange between nucleus and protoplasm leads to senility; anything which increases this interchange renews youth.

SOME MODERN PROBLEMS IN NUTRITION*

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PHYSIOLOGICAL chemistry is concerned with the chemical rearrangements which are constantly in progress in all living organisms. The continuity of these transformations is possibly the most striking characteristic of what we term "life."

Physiological chemistry finds its greatest support from the uses which practical medicine makes of its results, and thus to a large extent it has dedicated itself to the task of elucidating all the chemical changes occurring in the human organism. The most direct way to attack this extraordinarily complicated problem as a whole, is to make a comparison of the chemical composition of the organism's intake and output. Physiology has devoted itself, at enormous expense, to investigations aiming at the attainment of an exact metabolic balance. This method of investigation furnished chiefly quantitative results, for qualitatively it concerned itself with substances which, from a chemical point of view, were exceedingly ill-defined. By degrees, this drawback has been in part removed. For example, the main facts concerning the chemistry of the proteins have been recognized only during the present century.

Cellular material from plants and animals, especially mammals, constitutes the main source of our food-substances. Hence the study of these food-substances is closely allied to the chemical analysis of the human body, for the latter, considered from the standpoint of chemical classification, does not differ essentially from the animal food which supports it.

These descriptive studies, which we may regard as a sort of chemical anatomy of the human body, are essential for the

* Delivered March 22, 1913.

intelligent investigation of the chemical functions of the body. They are the more important, since the food-substances of the body are not utilized as is the fuel of an engine, whose parts are independent of its source of energy. In the animal organism, the food units have actually to furnish the ever-changing parts of the machine consuming them. The constant regeneration of these parts constitutes an important part of their chemical functions.

Anatomy and physiology are seldom so intimately united as when function and composition of cell aggregates are considered from a chemical standpoint. It is surely a sign of a lack of understanding when descriptive chemical studies of this character are regarded by physicians as purely chemical, simply because their biological significance is not obvious at the present time. It is true that pure chemists, without any biological interests, may take up work of this character and, indeed, they have done so in many lines of investigation. But often this has not been done, and then it is left for biology to till the ground, which may yield a harvest to succeeding generations only.

Metabolic physiology, using the term in the old sense, knew but little of the detailed structure of the food-substances. It concerned itself with the needs of the entire organism under the most varying conditions, with the availability, thermodynamic effect, value and utilization of the individual food-substances for various purposes. The experimental conditions were varied to include work and rest, hunger and satiety, foetal life, youth and old age, fever, subnormal temperatures and hibernation, the effects of high altitudes and sea-level, and so on. Valuable information was gathered in this way, but progress beyond a certain point was impossible, and from a purely chemical point of view, such studies were not particularly fruitful, for nothing definite was known as to what substances were qualitatively essential to the organism. Thus, meat which has been extracted with ether is lacking in a certain substance which cannot be replaced by the definitely characterized chemical substances of the ether-extract, and the

experimental animal, fed with such extracted material, ceases to thrive. Feeding exclusively with polished rice leads to a fatal condition with the development of symptoms similar to beri-beri. These symptoms may be quickly and completely abolished by the administration of about one milligram of a substance contained in that part of the rice which has been discarded. This substance belongs to none of the known groups of food-substances. What is it? Is it always necessary, or only in conjunction with a rice diet? We do not know. In questions of this nature, we feel our ignorance on every hand.

The methods of metabolic physiology in which only the gross effect is considered, can help us but little in obtaining an insight into these chemical changes, the elucidation of which promises an altogether deeper insight into the varied types of vital processes. The recent development of biochemistry has clearly shown that we stand only at the threshold of such new points of view. Historically, how much better off morphology appeared, which, having at its disposal highly developed optical methods of investigation, gave such an overwhelming stimulus to the tendency to consider all the problems of natural science from a descriptive point of view, that, for a time, it was believed that the most important problems of function could be solved by the microscope. Even now, in the education of medical students, we find descriptive methods still predominating to an extent which is only historically intelligible. Necessary as a knowledge of cellular structure is for the understanding of function, we must remember that, to quote the words of Hofmeister, the microscope shows us only the empty stage, the action on which is revealed to us only by totally different methods of research.

What is true for the individual cell is equally true for the whole body with its various organs. We are more and more struck by the fact that relations between different parts of the body are not exclusively controlled by visible morphological factors, and I need only mention the names adrenalin and secretin, pituitrin and iodothyroxine, to recall to your mind a series of organs about whose chemical functions we are par-

tially informed, but about which anatomical investigation has taught us almost nothing. Starling introduced the conception of hormones for these carriers of chemical impulses, among which may be mentioned the body causing the proliferation of mammary tissue following the injection of foetal extracts. Here, where the work of Jacques Loeb on the chemical stimulation of development is so well known, it is unnecessary to emphasize the prime importance of chemical studies with regard to processes which, in the past, have been relegated exclusively to morphological investigation.

The hormones which regulate the vital activities of the whole body are produced by the organism itself, and the chemistry of the formation of these substances must be altogether distinct from the normal breakdown of food material. We can hardly hope to understand these special reactions until we have attained an adequate picture of the normal catabolism of the substances which primarily furnish energy to the organism. Metabolic physiology has had little to say concerning these matters. It has indicated the possibility of the mutual replacement and possible interconversion of some of the main groups of food-substances, and it has shown that the conversion of protein, fat and carbohydrate to carbon dioxide, water, urea and sulphuric acid does not always follow the most direct path. But knowledge as to how these reactions occur and how they may be modified, can only be obtained from a detailed chemical analysis of these intricate changes, and at present our methods are inadequate for the task. If we consider as our first and final quest the formulation of equations which shall indicate, step by step, the gradual conversion of food-substances into the end products of metabolism, we shall find much that is helpful and stimulating. Oxidation reactions in the living organism are characterized by their slowness and regularity and the constancy of such conditions as temperature, pressure, reaction, etc., constituting a mechanism that we can hardly hope to imitate. It is the unique and extraordinarily complete character of this mechanism of the living

organism that makes it so generally interesting a subject for investigation.

After metabolic physiology had been for some time in a state of stagnation, the new ideas leading from a chemical conception of the intermediate paths of catabolism quickened the whole subject into renewed activity. Unsuccessful attempts had long been made to try to determine in the normal organism intermediate products, which would directly indicate the paths of normal metabolism. This is a most remarkable fact. We may perhaps understand this best if we assume that only a few molecules of a substance undergo oxidation simultaneously, and that their catabolism is complete before new molecules are attacked. Thus but few molecules will, at any one time, be in the first, second or third stages of oxidation, and the concentration of intermediate products of catabolism must always be low.

It was only when pathological or experimentally changed conditions were made use of, or isolated surviving organs were employed, or the fate of foreign substances in the body was investigated, that certain laws were developed, which subsequently proved to be applicable to the normal organism. Up to this time practically only hydrolytic changes, such as the breaking up of CO and CN groups with addition of water, had been observed. This type of change is seen in the conversion of protein into amino-acids with intermediate formation of albumoses and peptones, or in sugar production from starch, or fatty acids and glycerine from fats. But none of these reactions, which are effected by the digestive ferments, involve oxidation and they liberate no significant amount of energy and bring about no alteration in the chains of carbon atoms. The type of change involved in oxidation was first recognized in connection with the fatty acids, but even here, in spite of the fact that about 100 grammes a day may be burned, it was impossible to isolate intermediate products directly. When, however, a group resistant to attack in the body was introduced into the fatty acid molecule, it became possible to detect intermediate products. For this purpose phenyl substituted fatty acids were employed, the homologues of which

are found among the products of intestinal putrefaction and are constantly being absorbed. By using these substances, it was possible to show that fatty acids undergo oxidation in such a way that the oxygen invariably attaches itself to the β -carbon atom and the ketonic acid thus formed yields, on further oxidation, a saturated fatty acid, containing two less carbon atoms.

Thus it has been possible to determine the chief path followed by the fatty acids in their breakdown and to recognize the intermediate products which we are likely to encounter. This conception has led to an intelligible understanding of the origin of the acetone bodies from fatty acids in the diabetic organism. Similarly, the fact that the fatty acids, present in milk-fat, all contain an even number of carbon atoms, may be explained on the supposition that they are derived from one another by a process of β -oxidation. Many other examples of the helpfulness of this hypothesis might be cited.

It is of interest to note that the possibility of the above-mentioned physiological reaction was doubted by chemists, owing to the fact that such a reaction had not been observed in the chemical laboratory. The frequent observation of reactions and mechanisms in the living organism, which have not been hitherto observed, is certainly one of the stimulating attractions of biological research. This is especially true with regard to biochemical questions, since chemistry, perhaps more than any other science, has occupied itself with reactions, occurring in the test-tube without regard to natural processes. In many cases it is left to biochemistry first to unravel these intricacies by the investigation of natural objects. However, in the particular case with which we are concerned, Dakin was able to assist in its development and also to show that the hitherto unobserved reaction might be successfully imitated *in vitro*. This change was brought about by hydrogen peroxide, an agent whose action frequently closely resembles that of the animal oxidizing agents.

After a general scheme for the metabolism of fatty acids had been established, a successful attempt was made to gain

an insight into the mechanism of the cleavage of the amino-acids derived from proteins. This was done by using essentially the same method which had been helpful in the case of the fatty acids; that is to say, by the use of phenyl substituted homologues. The protein *Bausteine* or units are largely made up of amino-acids, all of which contain their nitrogen similarly linked to the α -carbon atom. This nitrogen may be split off in the form of ammonia, leaving an α -ketonic acid containing the radical—CO-COOH. The CO group, whether in the α or β position, forms a *punctum minoris resistentiae* for the action of oxidizing agents. It follows, therefore, that one carbon atom is removed as the first stage in the oxidation of α -ketonic acids, while the β -ketonic acids derived from the fatty acids part with two carbon atoms. Thus the amino-acids are converted into fatty acids, and these nitrogen-free radicals from proteins behave as fatty acids in their subsequent transformations.

In the course of these investigations upon fatty and amino acid catabolism, the behavior of a large number of hypothetical intermediate products, including ketonic and hydroxyl acids, unsaturated acids and acids with branched chains, and similar compounds, has been investigated and many valuable details have been discovered. Of these, I shall only mention the reduction processes by which ketonic acids are converted into hydroxyl acids, and even into fatty acids. For these results form the chemical basis for the comprehension of fat formation from sugar, a reaction which must clearly necessitate far-reaching reductions. Similar reactions lead to the reduction of aceto-acetic acid to β -hydroxybutyric acid, and we now believe, with Dakin and others, that aceto-acetic acid is the primary product from which β -hydroxybutyric acid is formed by secondary reduction. Formerly, the change was believed to be in inverse order.

One effect of these numerous discoveries has been to establish firmly the capacity of the animal organism for bringing about endothermic reactions, and furthermore, they have paved

the way to a revision of many traditional theories. A principle long held by Pflüger that carbohydrates could originate only from carbohydrate substances has had to be abandoned, as the result of numerous experiments, particularly upon diabetics. For we now know that other food-substances, such as protein, may yield carbohydrate, and American investigators have determined quantitatively the formation of sugar from a number of protein *Bausteine*.

The possibility of the reverse change, namely, the formation of protein from sugar and ammonia, was apparently excluded, for the statement that the nitrogen requirement of mammals could only be furnished by protein-like substance was regarded as one of the most firmly founded dogmas of the old metabolic physiology. But in connection with the foregoing question, I should like to show how valuable for metabolic physiology an exact inquiry into chemical detail may be.

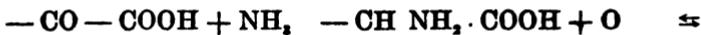
Every animal, even when overfed, constantly excretes in the urine a certain amount of nitrogen, which is derived from cell protein used up as the result of cellular functions. During starvation, this nitrogen minimum rapidly reaches a constant value, and, until recently, it was believed that this could not be influenced by inorganic nitrogen but only by protein. When it came to be recognized that protein underwent a far-reaching hydrolysis in the intestine, with the production of amino-acids, it was inferred, and subsequently proved, that these latter substances could maintain the nitrogen equilibrium, that is, the balancing of the nitrogen output in the urine by the nitrogen-containing substances of the food.

The capacity for synthesizing protein *Bausteine* from inorganic nitrogen was ascribed solely to plants, and amino-acids seemed to be the simplest substances capable of meeting the nitrogen requirements of animals. As a result of our knowledge of the cleavage of the amino-acids, we are now in a position to revise this question. May not the organism, after all, be able to utilize inorganic nitrogen, that is to say, the same ammonia liberated by the cleavage of amino-acids according to the first catabolic reaction already referred to?

The ammonia must, first of all, be brought into contact with substances which are formed simultaneously with it in the organism, such as ketonic acids. These experiments were successful, for it was found that the animal body can synthesize amino-acids from ammonia and ketonic acids, into which they may be reconverted later. The catabolic reaction is evidently reversible. We must therefore abandon the conception of differences between plant and animal chemistry, based upon the supposed inability of the animal body to effect syntheses. Ammonia is constantly present in small quantities in the animal body, and α -ketonic acids, which may react with it to give amino-acids, originate, as we know, not from fatty acids, but from sugar. We know relatively little of the oxidative catabolism of sugar, but we do know that in one way or another, lactic acid and pyruvic acid may be formed, and that both of these may be combined with ammonia to form protein *Bausteine*, especially alanine.

We are now in a position to understand the protein-sparing action of carbohydrates, while fatty acids yielding β -ketonic acids which are not convertible into protein *Bausteine*, have not the same action. Fact and theory agree. But now, if the reaction involving the liberation of ammonia from the amino-acids is reversible, one would expect that the administration of ammonia would influence the synthesis and exert a protein-sparing action. This theoretical deduction has been confirmed in a number of ways. Investigation by both clinicians and physiologists have shown that animals may be maintained almost in nitrogenous equilibrium for weeks at a time, with ammonia as their sole source of nitrogen. It would seem, therefore, as if the consumption of the protein material of the cells might be reduced almost to nothing, if only an excess of carbohydrates is administered.

I should like you to notice how the exact investigation of this single chemical reaction and the demonstration of the short equation:



together with other similar researches in intermediary metabolism has entirely revolutionized the teachings of the investigations of the laborious older metabolic physiology. No clearer proof could be offered of the value of exact chemical analysis in biological research.

Thus we see how products of intermediary metabolism may react with one another; for example, those from amino-acids with those from sugar. Doubtless also substances derived from fat, protein and carbohydrates may combine with one another. It appears probable that the synthesis of fat, following excessive consumption of other forms of food, may find its explanation in a process of reversible fatty acid catabolism. Possibly acetaldehyde or acetic acid compounds derivable from all of the three chief groups of food-substances may undergo condensation with formation of unsaturated or oxy compounds. These, in turn, may undergo reduction with formation of fatty acids with their long chain of carbon atoms. This type of reduction has already been observed in the case of benzoylpropionic acid and the corresponding unsaturated acids.

Another example of such a reaction has been noticed in connection with the synthesis of amino-acids in the animal body. It was found that an acetic acid radical may attach itself to the nitrogen group, but we are not yet fully informed as to the origin of this acetyl group. It will be noticed that this aliphatic group is combined in precisely the same fashion as are phenylacetic and benzoic acids combined with glycocoll in hippuric and phenaceturic acids. It would seem as if we were dealing with a reaction of general significance. Just as in the proteins the acid carboxyl groups are combined as acyl radicals with the basic amino groups, so we may picture the acid end products of fatty acid oxidation combining with amino-acids. Possibly our experiences with aromatic substances containing the benzoyl and phenacetyl groups may be found true in the case of their aliphatic homologues.

Whether the acyl radicals originate from the decomposition of sugar, for example pyruvic acid, or whether they come from aceto-acetic acid, is capable of experimental determination by

observing whether the yield of such condensation products is increased on feeding with fat or with carbohydrate. Should the mother substance of these acetyl groups prove to be the acetone bodies, which, as we know, do so much injury in the stages of acidosis in diabetes, it is possible that the feeding of easily acetylated substances may prove of therapeutic value. Such substances, perhaps, might take up considerable quantities of these acids in the form of acetyl groups and thus make them less harmful. Such a line of research should be of direct interest to the practitioner of medicine.

The more we succeed in unravelling the details of the chemical mechanisms of the animal body by tracing the individual reactions, the more likely are we to investigate successfully what we may call the bypaths of metabolism in which substances undergo reactions for other purposes than simply a liberation of energy. It is surprising to note how the smallest derangement of chemical conditions in the body may result in far-reaching injury.

We have a fairly clear picture of the reactions by which the pharmacologically active adrenalin may be formed from tyro-dioxide, methylation and the introduction of two hydroxyl groups. It has recently been shown that a number of substances contained in ergot which have long been used therapeutically, may be derived from different protein *Bausteine* by a similar reaction leading to the removal of carbon dioxide. The close chemical relation between food-substances and powerful poisons is very striking. It is through reactions such as these that toxins and other noxious bacterial products may be formed.

Almost all manifestations of disease have a chemical basis. But can we hope to comprehend these when we know so little of the normal chemical mechanisms of the organisms? Every branch of medical science is calling chemistry to its aid—pathology, internal medicine, bacteriology and serology. Pediatrics has become largely a study of the chemical pathology of nutrition, and even in such subjects as diseases of women and nervous diseases, progress is sought by chemical methods.

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In the universities of the Old World, new branches of learning, anxious to throw off restraints, progress but slowly. They must develop, as a rule, from existing departments which, owing to their own limited resources, are often slow to lend a helping hand. Time is required to bring about the needed changes. In this country of unlimited possibilities such restrictions need not be reckoned with and the favorable conditions we see here promise a development for our science that may soon rival that of Europe.

May our science and practical medicine flourish, and, rising above all personal and national considerations, serve the great cause to which we are all devoted—the welfare of mankind.

THE SCIENTIFIC BASIS FOR THE ARTIFICIAL FEEDING OF INFANTS*

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THE inability of many women to nurse their infants is usually regarded as an evil of modern growth and development. This is probably not the case, if one may judge from occasional references to the subject in the Bible, in the writings of Tacitus and elsewhere. But any particular mention in old literature of children is almost lacking, and they were not apparently matters of much concern to people in general until the last few centuries. The references to children before that time are almost entirely of a sentimental nature or by some moralist urging reform and regeneration, and inveighing against the wickedness of modern days. While we are informed that many mothers did not nurse their children, we cannot learn from the general diatribes whether it was because they could not or would not do so.

But whatever the reason why a woman did not nurse her infant, two methods have always been possible by which to supply him sustenance—the employment of a wet-nurse or some form of artificial food, in almost all instances the milk of a domesticated animal. Until the nineteenth century, the former of these was the only method of general application. For, if the prevalent superstitions, that a child might acquire from animal's milk some of the physical characteristics of that animal in the shape of a stray beard or horns, were disregarded, any slight experience with artificial feeding showed the direful consequences to the infant. It was a misnomer to call it "bringing up by hand" because in this way children were not brought

* Delivered March 29, 1913.

up. Apart from lack of information as to the quantity and quality of food, there was a total ignorance in regard to cleanliness. It seems strange, but not unlikely, that any form of artificial feeding would have failed in those days on account of the lack of proper utensils. Horns for bottles with sponges and pieces of perforated leather for nipples, hardly meet what we look on now as necessary requirements.

Artificial feeding was then, as now, chiefly necessary in cities, and the milk-supply of cities was absolutely bad. The unfortunate and diseased animals that furnished the milk were kept in the filthiest of buildings, often with no light or ventilation, were covered with sores and had usually for their only food the fluid refuse from breweries. But the evils of wet-nursing were so appreciable that a substitute for it was constantly sought and attempts were made with artificial mixtures of various kinds. Gradually, in a purely empirical way, the most unsuccessful of these were eliminated. But it was not until after the middle of the last century that artificial feeding was largely used. But anything more than empiricism has been of very recent date, and it is really only in the last twenty years that much that can be dignified by the word scientific has been learned about the nutrition of infants.

It would not be too much to say that the majority of artificial feeding has been done and still is done empirically, by rule of thumb, and with excellent results. Empiricism here has frequently shown the way before there has been satisfactory explanation of the *modus operandi* of some procedure, while, oftentimes, the explanation generally accepted has required revision though the fact established by observation has remained. Nevertheless, empiricism has also been responsible for the prevalence of many false ideas that have been rooted out only with great difficulty. Probably the reason for this is that the healthy infant has a great margin of safety. The flame of life, though small, burns fiercely within him. He will thrive at times under the most adverse circumstances and will withstand a great amount of well-meant but misdirected attention.

The distinction is not sharp between what may allow of satisfactory development and what produces it.

There is only one safe criterion of the proper food for an infant. It must so further his nutrition that he will leave the period of infancy and enter into that of childhood with an entirely normal mental and bodily development. If a decision as to the value of a diet were reached in this way, after long observation and with sharp criticism as to any deviation from the normal, there would not be so much difference of opinion as to proper methods. By clinical observation and not by physiological or chemical determinations must the superiority or inferiority of a diet or of a method of feeding eventually be established, and the acuteness of observers varies and their conclusions may be widely divergent.

When artificial feeding is begun, one of the first problems that presents itself is the total quantity of food that should be given to a normal infant, sufficient to supply his maintenance requirements and his requirements for growth. With the majority of breast-fed infants this does not have to be considered. The infant nurses until his appetite is satisfied, and the appetite and the quantity of milk are in most cases so nicely regulated that the demands of one are supplied by the other. But with the bottle-fed infant, the danger of overfeeding or underfeeding is real. The child's appetite, though still a guide, is not so much to be relied on, and what might be regarded as hunger is often discomfort from too much food.

How then are we to judge of his requirements?

The answer to this question has been sought in three ways: by metabolism experiments, by the determination of the energy exchange, and by the so-called "statistical method," or the balancing of the intake over long periods of time with the calculated output obtained by the occasional estimation of the excreta.

Metabolism experiments do not offer a satisfactory solution of the question for the chief reason that they can be of only short duration compared with the whole period of infancy. This would mean the application of the conclusions of a few

days to a period many times that length, the continuance of what might temporarily be borne to a point of intolerance and the multiplication of any false conclusion or trifling error to a substantial amount.

Metabolism experiments show excellently whether a food is distinctly deficient; they are not designed to show that an excess is given unless this excess is very great, and they are not at all well adapted to determine the food requirements.

Partly with the idea of determining food requirements, Rubner and Heubner first studied the energy exchange of infants with a Pettenkofer-Voit apparatus. In order to judge whether their results are to be taken as universally applicable, it is necessary to remember that the observations cannot be continuous. They must be interrupted every four hours in order that the infant may be fed, and once a day for a longer period. It is, therefore, impossible to make the determinations during more than twenty hours out of the twenty-four, and these four lost hours differ very greatly from the others in the activities that go on in them. The infant is much more active outside of his restraining frame than when in it. With the Pettenkofer-Voit apparatus the metabolism of quiet and active periods could not be separately measured, consequently it was assumed that there was not much difference between them and that the muscular activity of an infant had a negligible influence on the total metabolism.

Working with Dr. Lusk's calorimeter of the Atwater-Rosa-Benedict type, which was especially built for use with infants, I have shown that activity has an unexpectedly great influence; that crying increased the heat elimination of one infant 18 per cent, and that of another 39 per cent. It is very apparent, therefore, that if the determination of active periods is lost, the error may be a large one, and it is also apparent that the metabolism may vary greatly from day to day, according to whether the infant is especially quiet or especially active. It is quite obvious that experiments necessarily conducted in this manner cannot furnish the information that is required as to

the heat elimination of infants under normal conditions, and so the amount of potential energy that they require.

Determinations of the energy exchange may be made during sleep with a high degree of accuracy, using the modified Atwater calorimeter. I have made many such determinations and have obtained concordant results, provided the conditions were the same as to diet and that the infants were asleep. Any deviation from these conditions allows of no comparison between different infants or between different periods with the same one. With this method, then, we may obtain valuable information as to the effect of different kinds of food, of different environment and perhaps of different pathological conditions, but we cannot learn the total amount of energy that should be furnished the normal growing child.

The statistical methods consist in determining by actual weighing the daily intake of infants over long periods of time. A small number of observations have been made in this way by physicians, chiefly on their own children. Occasionally, the urine and feces have also been examined. But while the weighing is accurate, the variations in the composition of breast milk make it practically impossible to draw conclusions as to the total food value of the amount ingested, even if frequent samples are taken for analysis. The composition of breast milk is different to a marked degree at the beginning and end of each nursing period, and may be different at each period. If we rely on this method for information as to the total energy that should be furnished to an infant in his food, it makes a great deal of difference whether we consider, as Heubner did, that the caloric value of a liter of breast milk is 650 calories, or with Schlossman, that it is 782 calories.

The statistical observations have been almost without exception on breast-fed infants. It seems to me that there is a distinct opportunity offered to make the same observations much more easily and accurately on the bottle-fed, especially if the feedings are made up in a milk laboratory and the various ingredients are carefully measured. It would then only be required that the children should gain sufficiently and regularly.

They will not do it for a prolonged period of time in hospitals, and such observations are impossible there. Here is the chance for the practising physician to furnish information that may be of great practical use.

With all its sources of error this statistical method, which is really a refined empiricism, offers a better means of determining the average requirements of infants than do the others, and it is only the average that can be determined. No two infants even of the same size and weight have the same requirements. I have found that a healthy infant when asleep has a heat production of 1,094 calories a day, calculated in terms of square meter of body surface. But when infants are awake, a variable factor is introduced; for their activities are never the same, and these cannot be controlled and cannot be measured. For this reason it is never possible to say with certainty how much food any one particular infant will require. The problem of determining accurately the requirements of infants has not remained unsolved for lack of trying. The trouble lies in the inherent difficulty of the problem itself.

Before discussing the influence of various foods on digestion and metabolism, I should like to say that it is obviously impossible to give even a sketch of the whole field. I shall, therefore, confine myself to a consideration of those aspects that chiefly have claimed and do claim at present the attention of pediatricians. And I shall not attempt systematically to outline the uses of the food-stuffs or the transformations that they undergo, but rather to point out in what way it is believed they may be harmful and the proof that is brought that they are.

In the study of infant feeding it is to the several components of the milk that attention has especially been directed. The endeavor has been from the beginning to find out why it is that children fed on human milk thrive almost without exception in a satisfactory manner, while those that receive cow's milk may, oftentimes, do so badly that either extensive modification is necessary or a change to some other form of food. Ten years ago the answer to this seemed perfectly plain. Chemical analy-

sis showed as the most striking difference in the composition of the two milks that the protein of cow's milk was present in three times greater quantity than in human milk and that the proportion of casein to lactalbumin was much greater in the former. It appeared logical to suspect the casein as the substance most difficult of digestion and when Biedert, by means of reactions which cannot now be looked on as conclusive, determined what he considered to be undigested casein in the stools, it was generally assumed that the excess of protein in cow's milk was the explanation of the failure of cow's milk as a food for infants. In spite of the objections that were raised to this opinion, it was the prevalent one for many years, and has been given up reluctantly. For to a certain extent the belief seemed supported by the theory of Hamburger that "*artfremdes Eiweiss*" is an irritant to the especially sensitive cells of the infant's alimentary tract and that the necessity of breaking down the protein molecules to such simple substances that they could not be injurious after absorption, threw an added burden on the digestion, and one which was unnecessary with milk of the same species.

Support was also offered by some of the experiments of von Behring on the permeability of the gastro-intestinal tract of the young for bacteria and his insistence that finely divided casein could pass through the coarse filter of the intestinal wall. But the experiments of Bahrdt and Langstein on newly-born children have proven Hamburger at fault, for they have shown that the gastro-intestinal tract of the young does not treat in a different way "*artfremdes*" and "*arteigenes Eiweiss*"; it breaks both down to albumose in the stomach and to amino acids in the small intestine. Von Behring's views are also not possible of acceptance. If unaltered cow's casein were regularly absorbed, it would cause the production of an antiserum to cow's casein with the regularity that the parenteral injection of this substance does in experimental animals. Only in a few instances have precipitins for cow's milk been found in the blood of marantic children, by Moro and Brauer; but it is a very unusual finding compared with what one would expect

if the absorption of the unchanged casein were of frequent occurrence. And a certain degree of increased permeability in the very ill or moribund is not to be wondered at. Uffenheimer has emphasized the very perfect provision of the body against such an occurrence as the absorption of foreign protein by the prompt and complete precipitation of the casein by rennet in the stomach and of the protein substances out of the gastric contents, when they reach the intestine, by the cholates of the bile.

But it has been shown also that the observations of Biedert were false. The small white or yellowish masses which he considered to be undigested casein have been determined to be the insoluble soaps of the fatty acids, and indeed are much more frequently found with breast- than with artificial feeding. Adler has shown that the precipitate, the result of the addition of acetic acid in the cold, was not composed of casein, as Biedert and Albu and Calvo had insisted. The nucleoprotein of the intestinal secretion and the nucleoalbumin of the bile react in a like manner. He also showed that fasting stools contained a similar substance and that the minute quantities of albumin, albumoses and amino acids that were present were common to the stools of breast-fed and artificially-fed children alike. Numberless metabolism experiments have demonstrated, in addition, that the nitrogen of cow's milk is absorbed and retained, within the limits of experimental error, as satisfactorily as that of breast milk. The assumption, therefore, that cow's casein is difficult of digestion, appears in the stools as such and composes a "*Schädlicher Nahrungsrest*" is unsupported.

It should be mentioned, however, that casein does at times appear in the stools. The pretty experiments of Talbot have determined this. Occasionally when children are fed on raw milk, large bean-shaped, firm masses are found in the stools. These are largely composed of protein containing in its meshes neutral fat. The proportion of protein in these curds is so large as to make it impossible that it could come from the intestinal secretions, and Talbot was able to demonstrate that

the protein was casein by precipitin tests in which the dissolved protein was precipitated by anticow-casein serum, in the same way that pure cow's casein was precipitated, while no precipitate was obtained with other stools. Uffenheimer, later, also showed their biological character by anaphylactic tests, so that it may now be regarded as certain that cow's casein may appear practically unchanged in the stools. But that it has a limited if any pathological importance, but rather depends on physical conditions in the gastro-intestinal tract, may be assumed from the fact that these curds can be caused to disappear by boiling the milk, as a consequence of which the precipitation of casein by the rennet occurs in much finer flakes, and that infants passing even a large number of such curds present usually no evidences of discomfort or other derangements of digestion.

From numerous metabolism experiments it appears undoubtedly that, with this exception, the nitrogenous constituents of the food even when that food is cow's milk are completely absorbed and that the nitrogen of the faeces comes almost entirely from the intestinal secretions, and from bacteria. The nitrogen in 100 grammes of the dried faeces of the breast-fed infant is practically as great as that in the faeces of the artificially-fed, when allowance is made for the slight differences that occur from time to time with any feeding and with any child. Indeed, when equal amounts of protein are given, the amount of nitrogen may be greater with the breast-fed child, as a result of the excess of fat in breast milk, which causes an increase in the intestinal secretions.

From an examination of the stools, therefore, we obtain no clear indication that the protein of cow's milk is more poorly digested or absorbed than is that of breast milk.

But the chief interest attaches to the retention of the nitrogen. One of the most striking facts in this connection is the extraordinary eagerness with which all infants retain nitrogen. Growth is as normal and necessary a process for them as is the maintenance of equilibrium for an adult. The child's attempts to grow cease only with life itself. For this reason, he retains

nitrogen and the other substances necessary to form his protein material, if it is any way possible, and continues to do it under the most discouraging circumstances. Even when receiving a food the caloric content of which is insufficient for his requirements, he retains nitrogen and a not inconsiderable quantity of this, and burns his stored-up glycogen and fat to compensate for the lack of energy supplied in his food. Instead of utilizing all the food ingested to furnish energy as would the adult, he continues to use some nitrogen for growth and sacrifices other tissues of his body for this purpose. In other words he grows at the expense of his general nutrition.

This statement has been repeatedly proved by metabolism experiments, but clinically the fact is also appreciable, for children, not gaining or even losing weight, may continue to grow, at a diminished rate to be sure, but, nevertheless, to an extent that can be measured.

The protein food that is taken serves three purposes: first, it replaces that which has been used in the performance of the ordinary functions of the body and lost as desquamated cells, and as secretions; second, a small part is burned to furnish energy, and third, a distinct amount is retained for growth, often 50 per cent and even more.

It has been impossible up to the present time to contrive any experiments that will determine the amount used in the wear and tear of the body and that part destroyed for the production of energy. It is clear, however, that if the diet contains other ingredients in proper quantity and quality the amount of protein destroyed for these purposes is not large. The total amount of protein which is requisite, requisite and no more, is similarly undetermined. There is every reason to believe that the amount furnished to a healthy nursing infant represents at least a sufficient quantity and cannot be much in excess. As I have said before, it seems assured that cow's protein is not only digested as easily as human, but that the nitrogen of it is retained as readily, and it, therefore, appears not unlikely that other things being equal, less nitrogen might be required with cow's milk for the reason that nearly all of the

nitrogen of cow's milk is available for use, while only about 80 per cent of the nitrogen of human milk is available. The other 20 per cent is in the form of urea and extractives that can only be at once excreted in the infant's urine. I said other things being equal, for it is not beyond the bounds of possibility that it is advantageous to furnish an artificially fed infant some energy in the form of protein which may be at once used for the production of heat when the gastro-intestinal tract is especially liable to injury from the amount of fat and sugar necessary to produce the heat, with no help from the protein. Except for such a purpose, the protein requisite is strikingly small, and if we may accept the evidence furnished by breast milk, the protein does not require to be greatly increased after the first few months of life until toward the end of the first year. The chief demands for protein are to compensate for wear and tear, and to provide for growth, and as the one of these increases the other diminishes. Growth which is most rapid in the early months becomes less and less so, while as the body assumes a larger size, the wear and tear is greater. Thus it comes about that these two demands nearly balance one another throughout a large part of the first year.

The nitrogen retention of the normal infant is dependent to a great degree on the amount of protein food. After partial or complete deprivation of this, he retains a large amount for some time, when it is again offered, as if to make up for that which he had lost. If the protein continues to be given in excess, however, after a few days of very great retention, the retained nitrogen gradually diminishes day by day to an amount equal to that which would have been held, provided the infant had received the optimum quantity and no more.

But all of the other food-stuffs have an important influence on the retention of nitrogen. With a normal infant receiving enough food to meet his requirements the addition of fat to the diet in any form has no great influence. The addition of sugar or carbohydrates causes a much greater retention. The effect of a disturbance of digestion caused by either fats or carbohydrates is striking, especially when fat is the offending ele-

ment. A negative nitrogen balance is the result. The loss of nitrogen occurs not only in the faeces due to the greater amount of intestinal secretion, but in the urine as well, and to a larger extent. This loss of nitrogen is the result of changes in salt metabolism, for on the unfavorable influence of this the elimination of nitrogen chiefly depends.

The retention of nitrogen is also largely dependent on mineral metabolism. The retained nitrogen cannot circulate in the blood nor be loosely held by the tissues for any considerable length of time. It must be built up into living protein material and to do this salts must be available. Unless they are available the nitrogen is excreted again. Thus there must be a certain parallelism between the amount of nitrogen and the amount of total ash retained, and this has been found to be so. For every gramme of nitrogen about 1.7 grammes of ash are retained, not always at exactly the same time, but if the experiments are of long enough duration, these figures hold nearly true. A close parallelism between the retention of nitrogen and that of the individual bases cannot at present be shown, probably chiefly on account of the technical difficulties of the experiments, but also on account of the formation at different times of nitrogenous compounds now richer in one element and now in another.

I have already stated that it is the general belief that the protein of cow's milk is as readily utilized as is that of human milk. Is there then any possibility that it is injurious to the infant in the quantity in which it is given, usually two, three or four times as much as the breast-fed infant receives of human casein? Does this put an excessive strain on the organs transforming the products into eliminable form and those excreting these products? The only answer to this can be that no such injurious effect has ever been noticed.

There is a possibility, however, that a great excess of protein may, under certain circumstances, be harmful. Two calorimetric experiments that I have made indicate this. The heat production of one infant was raised 10 per cent. by an increase of protein in his food and that of another 26 per cent.

Moreover, it could be calculated in the case of the second child that all of the extra heat and carbon dioxide could not come from the protein alone, but that this protein, or more probably its decomposition products, acted as a stimulus to the metabolism of all the food-stuffs. This extra heat produced must be eliminated. Under ordinary circumstances, this is undoubtedly accomplished without difficulty. But if to excessive atmospheric temperature and humidity, factors preventing the elimination of heat, there is added the incurred burden of disposing of an excessive and unnecessary amount of heat, the possibility of nutritional disturbance may be increased.

Two other possibilities have been mentioned as factors causing failure in artificial feeding, one the formation of toxic decomposition products of protein and the other anaphylactic phenomena. The great size of the protein molecule allows of the formation of an enormous number of products, many of which are undoubtedly poisonous, provided the natural defenses of the body are inadequate. But nature has guarded against injury by them in a most thorough manner and though the possibility remains, proof that injury is caused is lacking. Moreover, Ernest Magnus has shown that, after all kinds of feeding, the intestinal contents obtained from an intestinal fistula may be toxic, except on a diet of milk, and then the toxicity is absent.

That anaphylactic phenomena are at all common with cow's milk feeding is much to be doubted. But that they occur as rarities seems likely. The only infant of which I have personal knowledge presenting such symptoms had regularly, severe vomiting after the ingestion of less than one ounce of cow's milk, with an intense urticarial eruption and collapse, and this was repeated as often as the cow's milk was given. No tests were used with this child, nor so far as I am aware have they ever been used to show a hypersusceptibility to casein in the same way that they were by Schloss to show a hypersusceptibility to white of egg. Hypersusceptibility in the biological sense cannot be used to explain the ordinary failures with artificial feeding.

Recently a series of interesting observations has been made by Drs. Holt and Levene and their coworkers on infants that had received a "synthetic" food very rich in casein. After a period of from four to six days on this diet, fever resulted and this continued until the food was stopped, when it immediately subsided. Interesting speculations are at once raised by these results, but they have little bearing on the question of artificial feeding, first on account of the artificial character of the food with its high sodium hydroxide content, and second, on account of the great quantity of casein given, greater by far than could be taken even in undiluted milk.

There is one other possibility that I should like to consider, and that is that a large amount of protein may play a not inconsiderable part in the production of the symptoms of what Czerny has called "*Milchnährschaden*," and which will be later discussed. It seems not improbable that some of the benefit to be derived from a change to a carbohydrate rich diet in this condition may be due no less to the limitation of protein, and thus of the putrefaction, than it is to the diminution of fats; at least some experiments that I have been conducting point that way. But when all is said, actual and possible, against the protein and especially the casein of cow's milk, it must be granted that it has so far lived down its evil reputation that it is generally regarded as a factor of but little if any importance in the general production of disorders of nutrition.

The differences of opinion that have been entertained in regard to the fat of the food, have been all as to the dangers of it and the disturbances that it might cause. There is unanimity in the belief that fat is beneficial for infants, and that those who, because of nutritional disturbances, cannot take a reasonable amount of it do not thrive so satisfactorily as do those who can. The very large proportion of fat in human milk indicates the amount of energy that advantageously may be provided by fat for the healthy infant. But the difficulty comes in furnishing this to the artificially-fed child without danger. It is necessary to emphasize "without danger" for the reason that the tolerance of infants for cow's milk fat

varies to an astounding degree. One will take even more than is found in human milk without a symptom and over a long period of time. This tolerance belongs especially to the older infant, though the very young may also exhibit it. Thus R. A. Cooke and I, in the course of some experiments, gave a boy of 10 months 76 grammes of fat a day for several weeks. He had no evidence of disturbance, his nitrogen partition was normal, with no increase of ammonia, he gained weight with rapidity and was comfortable.

But another infant, especially a young one, cannot take even a small amount without evidences of its harmful effects. Generally these evidences do not appear at once and, perhaps, only after a period of apparent benefit. Hence it has come about that there are widely divergent views as to the amount of fat that may be given with safety. To stay within safe limits is eminently the wise thing to do. For an intolerance to fat once established persists longer than an intolerance to any other food ingredient and compels the reduction of the fat to such a low point as to throw the burden of furnishing energy almost completely on the carbohydrates, and carbohydrates in excess are an insecure support for the young infant.

The digestion of fat and the effect of fat on the digestion of infants have been studied with great care by Tobler, Uffenheimer and others. Fats so retard the emptying of the stomach that stagnation may occur, and when the quantity is large, selective retention of the fat takes place. In marked instances of this, at the end of the day, it may be possible to obtain by the stomach tube almost all of the fat. But given such admirable opportunity for it, vomiting usually takes place. The strong odor of butyric acid suggests that the lower fatty acids are increased. Huldschinsky failed to obtain proof of this in persistently vomiting infants.

Though the presence of a fat-splitting enzyme in the stomach was definitely determined by Sedgwick, it probably plays a very small part, and the splitting of fats is accomplished chiefly in the intestine, and so completely, that under normal circumstances, not more than 1 per cent. of the fat escapes

this action. The further fate of the fats is not sufficiently understood. It would be of great assistance to know the form in which they are absorbed. Are they absorbed chiefly as fatty acids or as soaps, and if as the latter, as the soluble soaps of sodium and potassium or the insoluble ones of calcium and magnesium? Are the insoluble soaps the chief and most important means for the absorption of calcium and magnesium, or are they substances incapable of utilization? Are sodium and potassium driven out of combination with the acids, as has been suggested, and replaced by calcium and magnesium in the colon?

Much in regard to the form of fat even in the stools is denied us on account of the difficulty of separately determining neutral fat, fatty acids and soaps. So many methods have been employed each in itself more or less inadequate that a comparison of results obtained by different experimenters is hardly of value. The one good present method, Inaba's modification of the method of Kumagawa and Suto, allows the determination of only total fat. It may be said that approximately 40 per cent of the stool of the normal infant is fat, and of this, 10 per cent is neutral fat; about 10 per cent is soluble soaps and the rest fatty acids and insoluble soaps. The amount and relative proportion of each of these may be greatly influenced by circumstances and the absorption of fat may be similarly influenced. For example, while more than 90 per cent of the fat is absorbed under normal conditions, less than 50 per cent may be absorbed with severe diarrhoea of gastro-intestinal origin, and the neutral fat instead of being well split and forming only 10 per cent of the stools may form 40 per cent or more.

Fat was for a long time disregarded as a cause of harm to the infant. Biedert was one of the first to insist on the part that it might play in the production of diarrhoea, but it was Czerny's and Keller's experiments and writings and those of their coworkers that showed unmistakably that fat was a power for harm.

The most discussed and most studied of the conditions

ascribed to fat is that called by Czerny, "*Milchnährschaden*," which he says is synonymous with "*Fettnährschaden*." According to his view, the element responsible for this condition is the fat of the food. Increasing this fat makes the condition worse, and diminishing it makes it better. Infants with this condition are pale, and while perhaps fat, are pasty. Their appetite is poor, they gain in weight slowly, and finally not at all. The most striking thing, however, is the character of their stools. They are constipated. The stools are large, dry, light colored and foul, the so-called "*Seifenstühle*." The condition is amenable to treatment, and infants with this disorder usually respond rapidly to a diminution in milk and the addition of cereal and sugar especially in the form of one of the malt-soups, a combination of dextrins and maltose.

There are certain definite chemical changes with these "*Seifenstühle*." The nitrogen is somewhat increased, but the general retention of it is in no wise interfered with. The carbohydrates of the faeces are very much decreased, or rather, as Usuki has shown, these soap stools only occur when there is less than half of the carbohydrate in the stools that is ordinarily found. The fat is absorbed to a surprisingly good extent. It was held by Freund and others that the absorption was even better than under normal conditions, but the poor methods of analysis allowed this faulty conclusion. We know now that absorption suffers somewhat, but only to a slight extent, so slight, that a lack of sufficient nutritive material cannot account in any way for the clinical picture.

The positive evidence of harm is shown by the study of the mineral metabolism. It is the earthy alkalies that suffer most. Rothberg and Birk first pointed out this fact, the former for calcium and the latter for magnesium, and it has been shown since then over and over again. Why so much of these earthy bases is excreted is not clear. Bahrdt has calculated that much more calcium is passed in the stools than could be accounted for by the binding power of the fatty acids, but he was not able to determine the form in which this excess of calcium was lost. The fact remains, however, that the calcium and mag-

nesium are not retained. Whether this, the most constant and striking of the findings, is the only explanation of the poor condition of the infant and the failure to gain is not quite clear.

Stolte has pointed out that fat and calcium must be present in the food in considerable concentration in order that soap stools and constipation can result. But putrefaction is also necessary for the production of these stools as opposed to fermentation. Meyer and others have shown that the addition of casein may cause soap stools with evidences of putrefaction. But this excess of putrefaction only takes place when there is an insufficient quantity of carbohydrate in the food. If fermentation is active, putrefaction cannot take place and without this putrefaction soap stools cannot be formed. Usuki, in studying the partition of fat in the stools, found that when carbohydrate is present in the stool in any quantity, that is, when there is a substance that can ferment, soap stools are absent. If, however, the carbohydrate is in such quantity or of such quality that it is rapidly absorbed and therefore does not ferment, soap stools may be present.

There are three requisites for the production of these stools: at least a moderate amount of fat, casein and calcium in considerable quantity, and the absence of sufficient carbohydrate. This is an excellent example to show how complicated are the conditions in nutritional disturbances and how the food-stuffs interact, and how difficult and, indeed, unwise it is to consider one alone as the cause of any disturbance. The condition is usually considered a "*Fettnährschaden*." One could with nearly as good reason uphold the proposition that it is an "*Eiweissnährschaden*," while it is presumably more dependent on insufficient or improper carbohydrate than anything else. For the condition can be cured without reducing the fat and protein if the proper amount of suitable carbohydrates is added.

The diarrhoea caused by fat is quite a different condition. It is almost always acute and brings about chemical changes quite distinct from those just described. The endeavor was made by Salge to prove an association between a bacillus, the

acidophilus, with this condition, but without sufficient evidence. Racinski has shown in the breast-fed, and Langstein and Meyer in artificially-fed infants, an excess of lower fatty acids in the diarrhoeal stools. These, by their irritating effect, undoubtedly play an important part in the production of the diarrhoea. For a long time the cause of the high ammonia content of the urine could not be explained. Keller unavailingly sought for abnormal acids in the urine. Eventually, Steinitz demonstrated that there is a great loss of alkali, especially of sodium, by the bowel. The body is thereby so deprived of bases with which to neutralize the acids of intermediary metabolism, that ammonia must be furnished to take their place. The condition is therefore a relative acidosis. Though this increased ammonia was originally supposed to be due to the excess of fat, it is really quite independent of it, and occurs with diarrhoea due to any cause. Even with a severe diarrhoea the calcium and magnesium may be well absorbed and retained. So with these two disturbances that may be due to fat we have quite different chemical changes. One may run its course with a positive sodium and potassium balance, but with a loss of calcium and magnesium, the other with a positive calcium and magnesium balance, but with a loss of sodium and potassium. From their relative importance in the organism we would expect the condition in which calcium and magnesium loss occurred to be better and more persistently borne, and such is true of the clinical course.

The stormy condition sometimes met with as the result of feeding excessive quantities of fat, with sudden onset, high fever, repeated convulsions, persistent lack of appetite, vomiting and diarrhoea, has found no adequate explanation. It is for lack of a better name often spoken of as "acute acidosis" without evidence that the accompanying acidosis plays more than a secondary and subordinate rôle. Despite the lack of information in regard to it, the condition is a very serious and oftentimes fatal one.

In controversy, the battle usually rages thickest and hottest around some definite point. So it has always been with

the question of artificial feeding and so it is now. Proteins and fats are temporarily disregarded and the carbohydrates and salts are the objects of chief attack. With new knowledge and new hypotheses the assault is made from different quarters. The questions at present at issue are not at all those of ten or even five years ago.

Opportunity is given for a great difference of opinion in regard to the sugars and carbohydrates, because their fate in the organism is so little understood and the various intermediary products of their metabolism from the time of their absorption to their complete disintegration to carbon dioxide and water are quite unknown. It is thus not possible to follow these substances to the same extent that it is the proteins and the salts.

For the same reason opinions reached in regard to the carbohydrates must be largely the result of clinical observations. Now, while it is contended that clinical observations may have the same value as laboratory experiments, it can only be so when they are planned with the same care, conducted with the same adherence to technic and with the same avoidance of interfering, extraneous influences, and finally viewed with the same critical skepticism that the trained laboratory worker would employ. Usually these conditions have not been fulfilled, and for this reason from clinical observations absolutely contrary opinions in regard to almost any aspect of the question are obtained. To cite a few examples: It is claimed that lactose is absorbed from the intestinal tract very slowly and is therefore dangerous on account of the rare opportunity that it gives for fermentation. Again it is asserted that it is dangerous because it is absorbed so rapidly that lactose does not have an opportunity to break it down, and that, after its absorption as such, it acts as a poisonous and pyrogenic substance. Sainmont believes that he has demonstrated by observations on puppies that lactose is a much safer sugar than saccharose or glucose, while Heim came to a totally different conclusion. And in spite of the proof that could be brought against him, Weigert denies that milk-sugar has a nutritional value and insists that

as good results can be obtained with milk and cereal mixtures as with these plus milk-sugar. If one should rely entirely on published opinions, he would be left in a sad state of perplexity.

I do not wish to review matters concerning which there is complete unanimity of opinion, but I should like to emphasize, as so many others have done, the great dependence of the infant on the carbohydrates. He normally, and for his best advantage, obtains a large proportion of his energy from them. For a time he may disadvantageously exist with a minimum of carbohydrate food, but a lack of it very soon threatens life. So long as the infant with a nutritional disturbance retains a certain tolerance for carbohydrates, recovery may take place; but an entire loss of tolerance takes away the possibility of this. Especially in artificial feeding are the carbohydrates of importance; for the infant cannot take, or it is not wise to give him, the amount of fat that the breast-fed infant receives. The deficiency of energy must therefore be supplied largely by the carbohydrates.

There has been, and still is, much discussion as to the form of sugar which is to be preferred for infants. What one is most satisfactory as regards (1) tolerance, (2) influence on gain in weight, (3) influence on the absorption and retention of other substances, (4) influence as a corrective when nutritional disturbances exist, and (5) as regards safety.

The disaccharids are the only sugars ordinarily employed in infant feeding, the monosaccharids and polysaccharids have been used only for experimental purposes and need not concern us here. Of the disaccharids, lactose and saccharose are alone employed. Maltose is barred by its considerable cost. An especial place must be accorded to maltose in combination with other substances in the preparations known as dextrimaltoses, *nährzuchers*, malt-soups and various proprietary foods; but it must be recognized that maltose plays only a partial, perhaps an insubordinate, rôle in them. The mixtures contain a multitude of substances, known and unknown, maltose, salts, nitrogen-containing compounds and a great variety of dextrins and substances closely allied to them. And the beneficial results

following their use cannot be ascribed to any one particular substance.

It may be said in general that the limit of tolerance for sugars before mellituria takes place is very high in the normal infant. The sick infant, the feeble and premature and the eczematous may excrete sugar in the urine with a very small intake, but this sugar, so far as has been demonstrated, is almost lactose or galactose, rarely saccharose and never glucose, unless diabetes is present.

This tolerance is so high—Grosz, Nobécourt, Finizio, Aschenheim and others have shown this—as to put the danger of alimentary mellituria for normal children, with a reasonable intake, out of the necessity for consideration. This is the conclusion that one must reach even though different concentrations have been used and these have yielded different results. But these experiments give us no indication that either lactose or saccharose is superior. The limit of tolerance is about the same for both. That for maltose is twice as high, probably because maltose can be burned after passing the intestinal wall. Lactose and saccharose cannot be burned by the body cells, except apparently in very small quantity and after repeated injections, as Leopold has demonstrated for lactose. The tolerance for the maltose combinations has not been determined.

Under ordinary circumstances, all sugars act satisfactorily enough so far as gain in weight and a favorable influence on the retention of other substances is concerned. There is no convincing proof clinically or experimentally that one is superior to the other. They apparently furnish utilizable energy in the same proportion and their favorable influence on the retention of nitrogen seems to be the same, though experimental evidence for saccharose is almost lacking. After the first few months additional carbohydrates in other forms have a distinctly beneficial effect. Here the malt preparations may find application; but there is no proof that the normal infant may not thrive entirely satisfactorily without them, with the ordinary cereals.

It is, however, in the correction of nutritional disturbances

that a great difference between the sugars is seen. The disturbance described by Czerny and Keller as "*Milchnährschaden*," responds promptly to the malt preparations, especially when combined with cereals in considerable quantity, and this more or less irrespective of whether the amount of milk is reduced or not. To increase the lactose or saccharose unless they have been present in very small amount, is a dangerous method to bring about a similar result, because it may cause an excessive fermentation with severe diarrhoea. Maltose alone has no advantage over lactose or saccharose in correcting this disturbance as Usuki and Gerstenberger have demonstrated. It is equally if not more dangerous. It is the malt preparations combined with large amounts of cereals that are the most efficacious. Exactly why, no one knows. Usuki found after their use three or four times as much carbohydrate in the stools as when maltose alone was given, so that it might be said that the substance least utilized gave the best results. He believed that the beneficial effect was due to the slow, continuous and never rapid fermentation. On the other hand, DuBois and Stolte maintain that it is the potassium carbonate contained in the malt-soup that is of value, especially in preventing the excretion of calcium. It will take further experiments especially planned to decide this.

It is not so easy to determine what is the safest sugar. The difference of opinion here is very great. There is a tendency at the present time, even for many who were formerly warm in its praise, to accuse milk-sugar of being a dangerous substance even for normal infants, and of being the cause of most of the nutritional disturbances to which the infant is heir. The complaint is overdrawn. The satisfactory results with thousands in the past and at present prove this. Those who entertain these extreme views in regard to milk-sugar reach them as the result of hospital experiences in which hardly a normal child is ever seen. They forget the good results with healthy infants. Those who would deny milk-sugar any place in the dietary of infants must take the stand that it is dangerous only on account of its combination with cow's milk. For the milk-sugar of all

animals is identical and nutritional disturbances are most promptly and permanently cured by breast milk in which milk-sugar is in greater proportion than is found in any artificial mixture. It is, I think, a conservative conclusion that for the normal infant, lactose and saccharose, within reasonable limits, are by no means dangerous; indeed, they are probably safer in the very early months than malt preparations would be. When nutritional disturbances do arise, these sugars must be reduced or temporarily entirely withdrawn, and if introduced again into the food must be introduced only with caution.

There is ample evidence that the sugars can initiate trouble, especially in the feeble and those who have previously suffered from nutritional disturbances. Exactly how they do so is not clearly understood. The process is usually spoken of as fermentation, but the irritative and poisonous products of this have not been isolated. Von Bokay, Escherich and others, have incriminated the lower fatty acids formed from the carbohydrates. Certainly the lower fatty acids are in excess in the diarrheal stools, but whether they come from the sugars or the fats cannot be determined. Whether the effect is direct from products of sugar disintegration or indirect perhaps by action on bacterial growth, the result is the same. The food substances, especially the fat, are poorly absorbed, there is a loss of sodium and potassium salts as a result of the excessive intestinal secretions, so that a negative balance of these substances results and there is an excessive ammonia content in the urine.

I should like to postpone consideration of some of the other effects, including the pyrogenic effect, of the sugars, especially lactose, until the salts are discussed, because of their close association together in whey, which has been in the last few years accorded a prominent place in the production of nutritional disturbances of infancy. Mention, however, should be made of the carbohydrates other than the sugars because of their general employment during the latter part of the first year and of their beneficial effect even in early infancy. Of their *modus operandi*, little is known accurately. That they act to a degree like sugars is undoubtedly true, but clinical, and to a certain

extent chemical, testimony is to the effect that they have another influence. An infant may maintain his weight, neither gaining nor losing for many days or weeks, when only diluted milk and sugar are given to him. If then a small amount of cereal is added, improvement in general condition and in weight may take place at once. On a milk and milk-sugar mixture an infant may be losing calcium and magnesium. If a cereal is added, the negative balance becomes a positive one and may continue positive even if the sugar be entirely withdrawn. The beneficial influence is perhaps to be found in the constant slight fermentation and acid formation that results. Koltz has shown that a small amount of lactic acid by mouth had clearly an influence in improving the absorption and utilization of organic and inorganic compounds.

There is the thought that perhaps cereals made from the whole grain may have an additional value, but while this is suggested by the influence of polished rice on the production of beri-beri, it is a suggestion only.

As to the injurious effects of an excess of properly cooked cereal, we know very little in this country. The obscure condition known to the Germans as "*Mehlnährschaden*," with its disastrous outcome, is a clinical picture unknown to us. It is undoubtedly in part the result of hunger and nitrogenous and salt starvation, but whether the excess of cereal may also have a share in its production, is quite unknown.

The mineral metabolism of infants has been studied first to observe the effect of the increase or decrease of the mineral constituents, and second, as the means of determining the beneficial or harmful influence exerted by an alteration in the quantity or quality of the food. For in the ultimate analysis it is by the response of the mineral metabolism that we judge of the value of a food. It is the most sensitive indicator that we possess, and as such it is universally employed. There is, however, the very great disadvantage that under normal circumstances its behavior is very little known. There can be no doubt that normally, some of each of the mineral constituents is retained; yet in the literature there can be found less than a half

dozen experiments on breast-fed infants with complete, positive balances, and an equally small number on those artificially fed. In the great majority of metabolism experiments, on supposedly normal infants that have been published, one or more of the minerals has been excreted in greater amount than it was ingested. And, even when the balance of one mineral in a series of observations has been positive, the actual amount of it retained has been found to vary within extremely wide limits. The quantity that one considers should be retained is a question of personal belief and not one of demonstrated fact. For many decisions I believe that one period is not sufficient, but that two consecutive periods closely agreeing should be employed, and this, so far as I am aware, has practically never been done. Nor has it been shown, except very rarely, that two periods may closely agree. Perhaps it is true that the minerals are not continuously or regularly retained. It is much more probable that our experiments are not planned so that we can demonstrate this. For there are a good many possible sources of error. The infants are rarely normal infants, and the conditions under which the experiments are made are not normal. The observations have, in many instances, been too short, and the periods of collection of excreta not sharply differentiated. The urine may always be sharply separated. The stools seldom are, and there is the chance that too little or too much may be included in collecting. In the case of substances that are largely excreted by the intestines this fact may alter the meaning of the whole experiment. Furthermore, the change from one diet to another is often made too abruptly and the experiment begun immediately after the change without opportunity for the infant to become adjusted to the new conditions. A subsequent experiment on the same diet might give a very different picture. Thus, with a great increase in the nitrogen or of the mineral constituents of the food, there may be an excessive retention of these for several days, the retained amount, however, becoming less and less until a point is reached, not much if any, above what it was on a much lower diet. Conversely, on a change to an insufficient diet there may be a great

loss of nitrogen and salts; but as L. F. Meyer has demonstrated, this may be only for a time. The infant accustoms himself to a much lower level of metabolism and may even retain, in small quantity, nitrogen and salts, when losing weight. An early determination of his chemical balance would have given a totally erroneous impression of what the ultimate result would be, and one would have thought that he could go on losing minerals *ad infinitum*. It has been common to obtain one or two sets of figures and draw far-reaching conclusions from these which more careful observation would show to be quite unjustified. The literature is full of such conclusions. To explain some of these apparent contradictions it has been assumed that the infant possesses depots or stores of minerals that he may draw on during the first year at time of need, and that his body is therefore richer in some elements than it will subsequently be. This has not been proven except for iron, which, it is well known, his liver holds in excess. With this exception, from the time of birth until old age, the body becomes poorer and poorer in water and contains more and more salts.

The mineral metabolism of the artificially-fed differs greatly from that of the breast-fed infant. A comparison between the two is, therefore, well nigh impossible. The infant receiving cow's milk with its greater salt content, lives on a higher plane of mineral metabolism than does the one receiving breast milk. He absorbs 60 per cent of the total ash and retains only about 15 per cent, while the breast-fed child utilizes to the full his opportunities and absorbs 80 per cent of the ash and retains 40 to 50 per cent. In the majority of instances this excessive salt intake undoubtedly does no harm; the surplus is not absorbed or is merely eliminated.

It is to the earthy alkalies and the alkaline bases that attention has chiefly been directed during the last few years. I have previously indicated the influence that the various foods may have on them. Sodium and potassium are usually well retained, unless severe diarrhoea is present, due to any cause, an excess of fat or an excess of sugar. Under such circumstances they are lost, and the loss is badly borne and cannot

indefinitely be continued. When all available alkalies have been drawn on, the infant breaks down his own tissue to furnish more of these substances, which is an explanation, for a part at least, of the excessive nitrogen excretion under such conditions. When diarrhoea ceases and the intake is sufficient, a positive balance is rapidly instituted.

The metabolism of calcium has been largely studied on account of its close relationship to rickets and tetany. Calcium is so largely excreted by the bowel that it is impossible to say how much is absorbed, plays a part in the organism and is then excreted by the intestine, either because it is in excess or because, as in the case of rickets, the body cannot utilize it. This is also true of magnesium and to a much less extent of sodium and potassium. I have considered in detail the factors causing a retention and loss of calcium and the part played by protein, fat and carbohydrate. But in the study of the metabolism of rickets, these have rarely, if ever, been heeded. To cite a specific instance: In one study an infant on milk and cereal water was considered rachitic because he had a loss of calcium, and another fed on milk and malt-soup was considered non-rachitic because he retained calcium. In view of the work of Usuki and Stolte especially, the metabolism of rickets and tetany must be rewritten.

It was Finkelstein who first developed the conception that the sugar and salts of cow's milk, in the proportion in which they exist in cow's whey, were productive of much harm to the artificially fed infant, and were the cause of many, if not most, of the disturbances of nutrition. He emphasized that foods rich in whey were those on which infants developed their unfavorable symptoms, and that they were only cured by a diet in which cow's whey composed a minimum or from which it was excluded altogether. Finkelstein's contention seemed supported by Meyer's "*Austauschversuch*," in which he fed to the same infant human whey and cow's fat and casein, and later cow's whey and human fat and casein. When the human whey was given, the infant's digestion was normal and he gained weight. When cow's whey was given, he lost weight and

had marked diarrhoea. This experiment was claimed to prove the unfavorable influence of cow's whey. Stolte has criticised the conclusions drawn from it. He pointed out that the proportion of fat, protein and calcium was improper for the production of formed stools when cow's whey was given, while when human whey was given, there was ingested at the same time fat and calcium from the curd, in exactly the right proportion to produce formed stools.

It has been a fact generally known for many years that infants with acute nutritional disturbances excrete sugar in the urine when receiving milk of any kind. This is usually lactose. Such infants have more or less fever at the same time. From clinical observations Finkelstein and Meyer came to the conclusion that the sugar and salts that were allowed to reach the tissues of the body unchanged by reason of the diseased intestinal wall had a toxic and distinctly pyrogenic action. Contrary as was this belief to the general conception of the causation of fever, it obtained support from the experiments of Schaps. Schaps injected dilute solutions of lactose and sodium chloride subcutaneously and obtained a perfectly definite and more or less characteristic temperature rise, beginning four to six hours after the injection, reaching the maximum in eight to twelve hours and becoming normal again in twenty-four hours.

Since these results were published in 1906 a considerable literature, containing the results of a great number of experiments by different observers, chiefly in Germany, has grown up around the subject of sugar fever and salt fever. Febrile reactions have been obtained many times in different ways and a number of ingenious hypotheses have been proposed to explain the method of production of the fever.

In order to judge whether the results obtained are applicable to the question of infant-feeding and prove the dependence of fever and other untoward symptoms on sugars and salts taken in the cow's milk, let us consider how these experiments have been conducted. The sugars and salts have been given by mouth and by subcutaneous injection to normal infants and

those with nutritional disturbances. When normal infants have taken by mouth at one time as much as 30 grammes of sugar or even more, no fever results. At least this is the consensus of opinion of most of those who have experimented with them; and even when the huge doses were employed for the determination of tolerance, no mention was made of fever by Grosz, Nobécourt, Terrien, Keller and others.

With sick infants it is different. They will react, but by no means regularly; less than 50 per cent will do it. The temperature rise is not usually high; indeed, it is usually only slight, and it is somewhat delayed. The fever is found as often after large doses of glucose and saccharose, as after lactose and nearly as often after maltose. The quantity that produces this reaction is, moreover, very large, 30 grammes at one time, as much as the infant would otherwise take in the whole day.

It is difficult to see how such experiments can be expected to have any bearing on the question of infant-feeding or to prove the pyrogenic effect of lactose in the proportion in which it is found in cow's milk. They show unmistakably that concentrated sugar solutions have a bad effect on sick infants and this has long been known. More than this they cannot do.

Similarly with the various salts with which most of the experiments have been performed. Normal children do not usually respond with fever. Those who have been or are ill do so. But to produce fever, even with the sick, an amount is necessary that would at once indicate the impossibility of drawing any practical conclusions so far as nutritional disturbances are concerned. Indeed, doubt, and a very substantial doubt, is at once thrown on the part that these substances are claimed to play in such conditions. Thus infants of $3\frac{1}{2}$ kilos and less have been given in a day $5\frac{1}{2}$ grammes of sodium chloride, or 12 grammes of sodium phosphate, 5 grammes of sodium bromide, 10 grammes of calcium lactate, 10 grammes of calcium acetate and other substances in like proportion. The quantity at one dose has been 3 grammes and sometimes more. It is only fair to ask, as Salge has done, what such experiments are designed to investigate and prove, even if fever, collapse, vomiting,

diarrhoea, hyperglycæmia, mellituria and great loss of weight are produced. These studies are toxicological studies and have no bearing on the nutrition of infants. It is no wonder that febrile reaction occurs after giving at one dose in concentrated solution, six, eight or ten times as much of a substance as would be ingested under ordinary circumstances in a day and in a very dilute form. It is not at all improbable that similar or, perhaps, more disastrous results would follow the ingestion of a similar proportion of the other food ingredients provided they could be given at one time.

Injection experiments have seemed to offer more suggestive results. Schaps obtained fever regularly with minute quantities of sugar and salt in healthy and sick infants when given hypodermatically. Gofferjé, Möllhausen, Rietschel, Meyer and Schloss and many others had the same results. Weiland and Tjulpin were not able to produce fever and Friberger produced it in only one-third of his experiments. But the negative results were disregarded on account of the preponderance of the positive ones. The subject has been studied with great zeal, and the greater activity of sodium in combination with the halogens and the inhibiting effect of the divalent bases on the influence of the monovalent bases presumably established. But carefully conducted animal experiments lend no support to these views. Helmholtz and Schultz in this country, independently, investigated the effect of sugar and salt solutions on rabbits. Helmholtz could show no pyrogenic influence for salts nor could Schultz for sugars.

The studies of Wechselmann with salvarsan injections by which he showed that a febrile reaction frequently followed the use of distilled water if not immediately sterilized, and that the febrile reaction was absent if sterilization closely followed distillation, offered another field for inquiry. So also did the studies of the Lister Institute of Preventive Medicine in London, where it was demonstrated that salt solution or water is not free from pyrogenic properties even after all organisms have been destroyed by heat. Samelson, therefore, made a series of experiments with children less than 3 months of age,

when they are supposed to be most likely to react. He used 20 to 80 c.c. of an 0.8 per cent sodium chloride solution freshly distilled and freshly sterilized, in all, seventeen times. No fever was ever produced and none of the other symptoms usually following injections. Fever was frequently produced when ordinary distilled and sterilized water was employed. The results that Bendix obtained were even more instructive. He injected seventeen infants with 50 c.c. of 0.75 per cent solution of salt and produced fever fifteen times. He then found that the water that had been used had been distilled the evening before and not been sterilized until twelve hours later. He therefore repeated his experiments, using freshly distilled and freshly sterilized water, and produced no fever and no symptoms in any single case. It appears, therefore, that there is no satisfactory proof that sugar or salt hypodermically has a pyrogenic effect, and that experimental evidence that would show that the sugars and salts of the whey are responsible for fever and the chain of constitutional symptoms associated with it, is lacking. It may be that they act indirectly in injuring the cells of the intestinal tract so that other substances, perhaps bacterial, are absorbed. It may be that they act in a variety of other ways, but their own direct and damaging influence has not been proved, and has been, undoubtedly, greatly overemphasized.

The reasons for the difficulties or the failures with artificial feeding are at times sufficiently apparent. At others no fault, so far as one's experience goes, can be found, and yet the result may be far from satisfactory. This is more apt to be true of methods designed to correct some existing disturbance than it is of those employed with the normal infant. What is the explanation of failure with these?

Biological reasons have been offered and the influence of the prevalent views of workers in biological laboratories is reflected in these reasons. I have already referred to Hamburger's views on "*arteigenes*" and "*artfremdes Eiweiss*," and the effect that the latter might exert on the immature organism. This was when the distinction was drawn between homol-

ogous and heterologous compounds. In recent years the idea of anaphylaxis has crept into the discussion. This has been equally incapable of shedding light on the ordinary problems of nutrition. The diatheses have, therefore, been called on. Here we enter a very large and indefinite field.

The conception of diatheses first arose in an endeavor to explain the different degree of susceptibility and the different resistance manifested toward infection. Now they are used in questions of nutrition to explain what cannot be accounted for on a purely chemical basis. These diatheses are not sharply defined. The "scrophulous diathesis" has gradually disappeared, its place to be taken, in the non-tuberculous cases, by the "exudative diathesis" of Czerny. A lymphatic diathesis has been described, a thymico-lymphatic, an arthritic and a neuro-psychopathic. The French have different classification from the Germans and no two authors agree. If a conception to one seems too narrow it is broadened by combining two diatheses, as in the neuro-lymphatic; and finally all possible constitutional abnormalities and predispositions have been massed together and called "*Oxypathie*" by Stoeltzner.

The only diathesis, except for the pathological status thymico-lymphaticus, that rests on a tangible basis is the "exudative diathesis" of Czerny. It has been shown that infants exhibiting symptoms of this usually utilize their ingested fats less well than the average and that their symptoms are increased by fat; that they have frequently hyperglycæmia and alimentary mellituria, even with a small carbohydrate intake, and that they show a marked tendency to retain salt and water in their tissues. It is a question, however, how much light this conception of diatheses has brought to the subject that now interests us; probably not much. It has certainly tended to confuse.

We are thus left without an adequate explanation for many difficulties and many failures. This gives an incentive for future work.



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